THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1958

ORIGINAL ARTICLES

ON THE ANTICATABOLIC AND ANTICALCINOTIC EFFECTS OF 17-ETHYL-19-NORTESTOSTERONE

By Hans Selye, M.D., D.Sc., Ph.D.
PROFESSOR AND DIRECTOR, INSTITUT DE MEDECINE ET DE CHIRURGIE EXPERIMENTALES

AND

Serge Renaud, D.M.V.
RESEARCH ASSISTANT, INSTITUT DE MEDECINE ET DE CHIRURGIE EXPERIMENTALES

(From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada)

Numerous early clinical observations suggested that there is some close relationship between male hormones and somatic growth. For example, owing to their ability to stimulate not only somatic growth in length, but also muscular development, virilizing adrenocortical tumors have often been seen to elicit the "Infant Hercules" syndrome in children. Later, when synthetic testosterone became available, it could be shown by experiments on the rat that this hormone stimulates somatic growth (especially in females); hence, it was concluded that the anabolic effect of virilizing tumors is presumably due to the testoid or "androgenic" hormones that they produce (McEuen, Selye and Collip[3]). Subsequent investigations revealed that numerous other testoids exert similar effects, both in animals and in man; these actions have variously been described as anabolic, anticatabolic or nitrogen-retaining. (For literature see Selye[4,5], Selye and Heuser[6], Selye and Horava[7,8]).

The prevention of catabolism and the enhancement of anabolism by comparatively nontoxic steroid hormones would be of considerable clinical importance, for instance, in convalescence; but, the practical use of these substances is greatly curtailed by their virilizing effects. A great deal of attention has been given, therefore, to comparative bioassays of the anabolic and testoid properties of steroids, in the hope that compounds will be found which, though strongly anabolic, possess little or no testoid side-effects. Large-scale screening programs of this type are greatly handicapped, however, by technical difficulties inherent in such bioassays. It is time-taking and costly to perform accurate nitrogen-balance studies on large numbers of small laboratory animals and the somatic-growth (or weight) stimulat-

ing effect of these compounds is not sufficiently pronounced to serve as a basis for sensitive bioassays. Attempts were made to assess the anabolic actions of steroids by the weight increment which they produce in randomly selected, individual skeletal muscles, but they also proved to be rather insensitive indices. It was then noted that certain muscles, notably the temporal muscles of the guinea pig (Kochakian and Tillotson[2]) and the levator ani of the rat (Drill and Saunders[1]) are unusually sensitive to stimulation by anabolic steroids. However, tests based on these indicators of activity are likewise unsatisfactory, precisely because these particularly sensitive muscles do not reflect the reactivity of the skeletal musculature in general.

Recent studies showed that methyltestosterone is highly effective in counteracting the catabolic (or antianabolic) effects of various stressors. Among all the toxic agents tested, the catabolism induced by two vitamin-D derivatives (dihydrotachysterol and vitamin-D_2) was conspicuous by being most markedly inhibited as a result of methyltestosterone treatment. Perhaps here, the ability of methyltestosterone to inhibit soft-tissue calcification (such as occurs in hypervitaminosis-D) complements the nonspecific anticatabolic action of the steroid. In any event, it was thought that the inhibition of body-weight loss during hypervitaminosis-D may offer a simple and highly sensitive indicator of the general anticatabolic action of steroids (Selye and Mishra[9]).

Since 17-ethyl-19-nortestosterone (Et–19NT) (Nilevar) proved to be a highly active anabolic steroid in man (Spencer *et al.*[10]), we decided to compare its anticatabolic and, incidentally, also its anticalcinotic effect with the corresponding actions of the relatively more virilizing methyltestosterone (Me–T), in rats intoxicated with dihydrotachysterol (DHT).

Materials and Methods. Two experimental series were performed under essentially similar circumstances. In the first, 70 female Sprague-Dawley rats, with an average initial body-weight of 100 gm. (range: 90 to 112 gm.), were subdivided into 7 equal groups and given Me–T or Et–19NT, simultaneously with DHT, at the dose-levels listed in Table 1. In the second series, 70 female Sprague-Dawley rats, with an average initial body-weight of 107 gm. (range: 98 to 113 gm.), were similarly treated with Me–T and Et–19NT, but here in order to determine whether the actions of the anabolic steroids would be more evident after a period of pretreatment, the administration of DHT was started only on the third day of the hormone injections.

In both experiments, all doses of *Me–T* and *Et–19NT* were administered in the form of microcrystal suspensions, in 0.2 ml. of water, subcutaneously, once daily, while *DHT* was given as a microcrystal suspension, at the dose of 300 μg. in 0.5 ml. of water, by stomach tube, daily.

Throughout the period of observation, all animals were kept exclusively on "Purina Fox Chow" and tap water.

Both experiments were terminated on the 14th day after initiation of the hormone treatment, by killing the animals with chloroform.

The *anticatabolic effect* of both Me–T and Et–19NT was quite evident in both series, as judged by the body-weight of the animals at the end of one week. However, for the sake of simplicity in the Tables, only the final body-weights are listed. In the second experimental series, we also determined the weights of the totally eviscerated carcasses (both the thoracic and the abdominal cavities were totally emptied) in order to eliminate any accidental variations in weight that might be due to the rather variable volume of the intestinal contents. The kidneys were weighed only in the second experiment, and served as an example of anabolism in a nonmuscular parenchymatous organ.

In both experimental series, the degree of soft-tissue *calcification* was assessed in terms of an arbitrary scale of 0 to 3, both macroscopically (inspection with a magnifying glass) and microscopically (von Kossa's silver nitrate technique on neutral-formalin-fixed, paraffin-embedded sections). The severity of the calcium deposition was thus appraised in the heart, the aorta and kidney of each animal

and the means of these readings are given in the Tables.

The weight of the *preputial glands* was taken as an approximate indicator of testoid activity.

In the Tables, the means of all these measurements are listed, together with the corresponding standard errors.

Results. There appears to be no great advantage in commencing steroid treatment prior to the administration of DHT, because, as perusal of the Tables shows, both experiments gave approximately similar results. For this same reason, we shall discuss the data of the 2 series conjointly.

It is evident that, at all dose-levels used, both Me–T and Et–19NT exerted anticatabolic, anticalcinotic and preputial-gland stimulating effects. The anticatabolic and anticalcinotic actions of Et–19NT proved to be superior to those of Me–T, although this difference was not statistically significant at all dose-levels. On the other hand, there was no statistically significant difference between the preputial-gland stimulating effect of Me–T and Et–19NT at any dose-level, in either of the 2 experiments.

Discussion. It appears that rats given toxic doses of DHT are suitable test-objects for the bioassay of the anticatabolic and anticalcinotic actions of steroids. The gross final body-weight, the weight of the eviscerated carcass and the renal weight all reflect the anticatabolic effect. However, if a single indicator only is to be used, the eviscerated carcass might well be selected, because its weight increment under the influence of the steroids is at least as great as that of the whole body, while

TABLE 1.—EXPERIMENT 1 IN WHICH DHT WAS ADMINISTERED SIMULTANEOUSLY WITH ME–T OR ET–19NT

Group	*Treatment*	*Final Body Weight (gm.)*	*Calcification (Scale: 0 to 3)*	*Preputial Glands (mg.)*
I	None	87±3.9	1.5±0.36	49± 4.4
II	Me–T (100 μg.)	96±5.8	1.2±0.36	148±14.2
III	Me–T (1 mg.)	105±2.2	0.7±0.26	188±13.7
IV	Me–T (3 mg.)	133±8.5	0.7±0.33	238±23.0
V	Et–19NT (100μg.)	111±5.1	0.5±0.24	147±15.3
VI	Et–19NT (1 mg.)	128±6.9	0.4±0.2	205±13.2
VII	Et–19NT (3 mg.)	133±5.6	0.2±0.07	208±15.2

TABLE 2.—EXPERIMENT 2 IN WHICH ADMINISTRATION OF DHT WAS BEGUN ON THIRD DAY OF HORMONE INJECTIONS

Group	*Treatment*	*Final Body Weight (gm.)*	*Eviscerated Body Weight (gm.)*	*Renal Weight (gm.)*	*Calcification (Scale: 0 to 3)*	*Preputial Glands (mg.)*
I	None	91±2.4	66±1.4	729±30.5	1.6±0.17	31± 3.1
II	Me–T (100 μg)	105±5.0	77±3.9	795±30.7	0.8±0.30	72± 6.7
III	Me–T (1 mg.)	131±5.2	101±4.1	937±36.1	0.4±0.17	198± 9.0
IV	Me–T (3 mg.)	132 6.0	98±5.1	904±36.4	<0.1	208±12.6
V	Et–19NT (100 μg.)	129±3.6	97±2.7	890±37.3	0.6±0.25	68± 5.7
VI	Et–19NT (1 mg.)	149±4.5	114±3.1	1002±45.7	<0.1	176± 9.0
VII	Et–19NT (3 mg.)	142±4.5	109±3.5	1131±47.1	<0.1	183± 8.7

its standard error is smaller than that of the gross body-weight at all dose-levels. The renal weight is also a sensitive indicator of anticatabolic steroids, but the response of the kidney does not reflect somatic anabolism as accurately as does the carcass weight, because nephrosclerotic steroids and, perhaps also, strongly renotrophic steroids might cause a disproportionate renal enlargement.

It is evident, furthermore, that at the daily dose of 1 mg. or more, both Me–T and Et–19NT almost completely prevented the soft-tissue calcification normally induced by DHT overdosage. This effect is particularly striking, as regards the inhibition of the

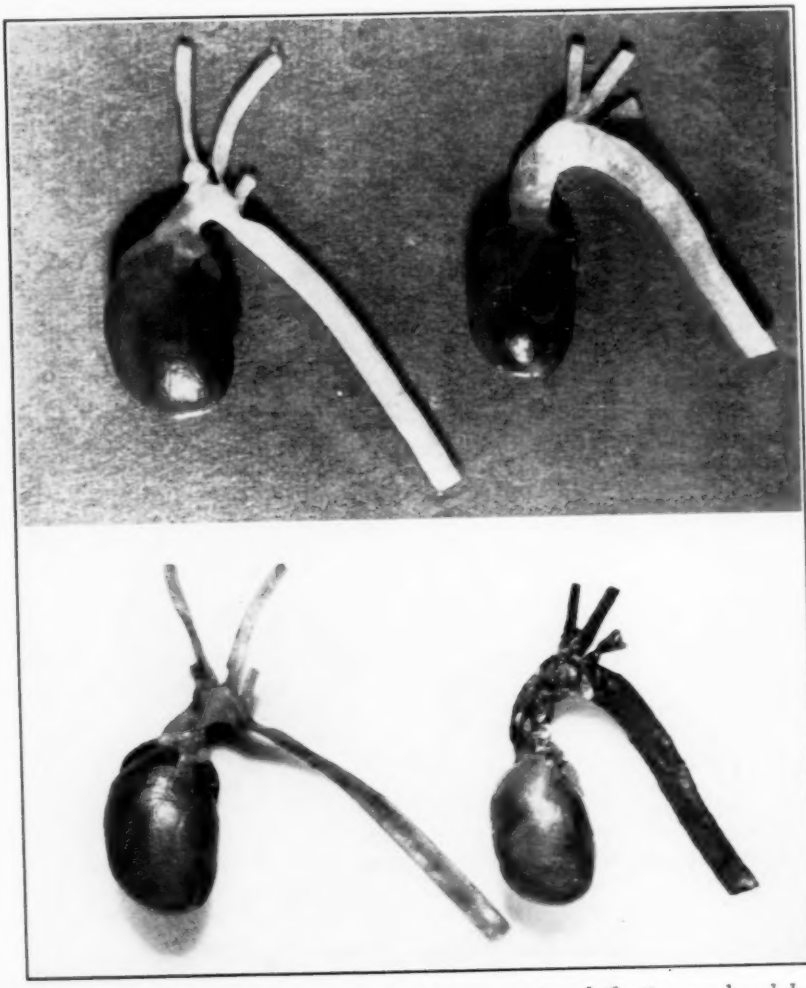

Fig. 1.—*Protection by ET–19NT against the intense aortic calcification produced by DHT.* Both rats were treated with the same dose of DHT, but only one (left) was simultaneously given 1 mg. per day of ET–19NT, *Top:* Photograph of the fresh preparations. *Bottom:* Same preparations after blackening of the calcified areas, by immersion in silver nitrate and subsequent exposure to light.

Mönckeberg-type of arteriosclerosis that is normally caused by DHT (Fig. 1). It remains to be seen whether the steroids that protect rats against this type of vascular damage would affect other experimental and clinical arterial diseases, but in future bioassays in which our technique is employed, it may be well to determine not only the anticatabolic, but also the anticalcinotic action of the compounds tested, since this interesting side-effect can be assessed so easily by mere inspection with a magnifying glass.

The greatest weakness of our anticatabolic assay technique is that here, the prevention of a body-weight loss may largely be due to the ability of certain steroids to counteract the specific toxic effects (calcinosis) of DHT, and we have no proof that this action is related to anticatabolic activity as such. Therefore, it would seem advisable to use this test only for large-scale screening and to re-assay the most potent steroids for their ability to counteract the catabolism produced by other stressors, for example, those which we employed in our earlier work on the anticatabolic effects of methyltestosterone (Selye and Mishra[9]). However, since the catabolism induced by DHT proved to be more readily inhibited by steroids than did that caused by other noxious agents, the anti-DHT test, as here described, appears to be the bioassay of choice for the first orientating experiments. The advantage of the anti-DHT test over nitrogen-balance studies lies in its simplicity and in the fact that, unlike the temporal-muscle or levator-ani-test, it measures anticatabolic actions in general and not the specific effect of steroids upon certain muscle groups that are known to respond differently from the bulk of the skeletal musculature.

Summary. Both methyltestosterone (Me–T) and 17-ethyl-19-nortestosterone (Et–19NT) are highly active in preventing the catabolism and the soft-tissue calcification that normally occur following intoxication with dihydrotachysterol (DHT) in the rat.

In both these respects, Et–19NT appears to be only slightly superior to Me–T.

The preputial-gland-stimulating effect of the two testosterone derivatives is essentially the same at all dose-levels tested, but it must be kept in mind that these glands do not reflect testoid activity accurately.

The advantages of the anti-DHT-test for the evaluation of anticatabolic compounds are compared with those of other bioassay methods in current use.

ACKNOWLEDGMENTS: This work was aided by grants from the Muscular Dystrophy Association of Canada; the Medical Research Board, Office of the Surgeon General, Department of the United States Army, Contract No. DA–49–007–MD–186; the Squibb Institute for Medical Research, and the Pfizer Laboratories.

The authors also wish to thank the Schering Corporation Limited for the methyltestosterone (Oreton-M), G. D. Searle & Company for the Et–19NT (Nilevar), and Dr. A. Wander S.A. (Berne) for the dihydrotachysterol (Calcamin) employed in these investigations.

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SUMMARIO IN INTERLINGUA

In Re Le Effectos Anticatabolic E Anticalcinotic De 17-Ethyl-19-Nortestosterona

Methyltestosterona (Me–T) si ben como 17-ethyl-19-nortestosterona (Et–19NT) es altemente active in prevenir le catabolismo e le calcification de histos molle que occurre normalmente in rattos post intoxication per dihydrotachysterol (DHT).

In ambe iste respectos, Et–19NT non pare esser plus que levemente superior a Me–T.

Le effecto stimulatori super le glandula preputial exercite per le duo derivatos de testosterona es essentialmente le mesme pro omne le nivellos de dosage essayate, sed on non debe oblidar que iste glandulas non reflecte le activitate testoide accuratemente.

Le avantages del test de anti-DHT in le evalutation de compositos anticatabolic es comparate con illos de altere methodos de bioessayage de uso currente.

SUMMARIO IN INTERLINGUA

(See page 23 for original article)

Le Condition Del Hospite Como Factor Afficiente Le Crescentia De Streptococcos Hemolytic B in Le Pharynge Human: Un Studio Preliminari

In le 3 familias studiate il esseva apparente (1) que, in despecto de lor exposition intime a streptococcos hemolytic beta, non omne individuos demonstrava le presentia de iste organismos in culturas, (2) que alterationes in le flora bacterial del pharynge non esseva explicabile super le base de factores como exposition, climate, pH, o color del pharynge, e (3) que un correlation pareva exister inter le stresses que afficeva le familias como gruppos e le apparition de culturas positive. In iste correlation, il pareva que le patre esseva un figura central. In un del casos le aspectos pertinente del situation esseva que le patre esseva irritabile e exigente in consequentia de stresses que ille habeva experientiate, e le plus vulnerabile individuos esseva apparentemente illes qui se sentiva le plus insecur in lor relation con le patre. Le datos non permitte un presentation definitive de iste formulation. Illo es tentative e require un corroboration futur.

PHENOLIC COMPOUNDS IN CHEMOTHERAPY OF RHEUMATIC FEVER*

By Norman E. Clarke, M.D.

Charles N. Clarke, M.D.

AND

Robert E. Mosher, Ph.D.

(From the Department of Research, Providence Hospital, Detroit, Michigan)

The treatment of rheumatic fever has been little improved in 80 years or since salicylic acid was introduced to become recognized as so specific that its actions bespeak a particular chemical structure complementing a unique pathological condition.

It has not been possible to reproduce more than experimental approximations of rheumatic fever in animals. We treated human subjects who had rheumatic fever that met the Jones Criteria requirements. The comparative chemotherapy was based on the classical concept of investigating compounds chemically related to one that manifests therapeutic activity. The antirheumatic action of the monophenol salicylic acid was established so we investigated related compounds hoping to find one with greater potency, minimal toxicity and that might prevent heart damage.

We investigated the 3 monophenols which include salicylic acid and also 5 diphenols and 2 triphenols that are chemically related.† The several compounds were compared by their ability to suppress the manifestations of rheumatic fever, toxic reactions, and prompting of detoxifying mechanisms.

Materials and Methods. The phenolic acids excreted in urine were determined by the colorimetric procedure of Gerald and Kagan[6]. This procedure was developed for gentisic acid but was reliable for other phenolic acids in urine and blood serum. The estimation of total drug content in urine specimens was made as follows: We pipetted 5 ml. of dilute hydrochloric acid (2 to 5%), boiled gently for 20 minutes then cooled and neutralized with reagent grade calcium carbonate. The solution was transferred quantitatively to a 250 ml. volumetric flask, diluted to the mark and mixed thoroughly by inversion. The excess calcium carbonate was allowed to settle and a 5 ml. aliquot of the clear supernate pipetted into an Evelyn colorimeter tube, 5 ml. of the ferric-ferrous chloride reagent added and the optical density of the resulting solution measured in an Evelyn colorimeter tube at a wave length of 660 millimicrons using a reagent blank. The colorimetric standards were based on solutions of specially purified compounds. Preliminary trials with standard solutions of the phenolic acid were done to determine any loss of compound due to decarboxylation under the conditions of hydrolysis described.

The urinary glucuronic acid levels were determined by the Tollens' or naphthoresorcinol colorimetric method as modified by Fishman and his co-workers[5] and the urinary

*This work was supported in part by Grants in Aid from the Michigan Heart Association and Matilda Wilson Rheumatic Fever Fund.

†The beta resorcylic and pyrocatechuic acids were provided by Koppers Corp., Pittsburgh, Pa.; phloroglucinol carboxylic acid by Ringwood Chemical Corp., Ringwood, Illinois, and gamma resorcylic acid, 2, 3, 6-trihydroxy benzoic and 2, 3-dihydroxy benzoic acids were synthesized by Lark Research Laboratories, Detroit.

ethereal sulfate levels by the gravimetric procedure described by Hawk, Oser and Summerson[9].

Salicylic Acid. In salicylic acid the single hydroxyl (OH) group on the benzene ring occupies a position adjacent or ortho to the carboxyl (COOH) group. In one of the 2 isomers of salicylic acid the hydroxyl group is in the 3 or meta, in the other 4 or para position. Of 3 possible monophenols only salicylic acid forms a chelate ring with its hydroxyl group sharing its hydrogen ion with the adjacent ketone of the carboxyl group and producing unique ability to suppress rheumatic fever manifestations but also distressing toxic reactions. The 2 isomers of salicylic acid, not forming chelate rings do not have antirheumatic action.

Gentisic Acid. Gentisic or 2,5-dihydroxy benzoic acid is a metabolite of salicylic acid (Clarke, Mosher and Clarke[3], and Meyer and Ragan[14]) and has the same chemical structure plus a second hydroxyl group in the 5 or para position. The 2 hydroxyl groups permit the formation of a chelate ring and a reversible quinone-hydroquinone system. In a previous paper (Clarke, Mosher and Clarke[3]) the treatment of patients who had monocyclic, polycylic and persistent forms of rheumatic fever demonstrated that gentisic acid excelled the salicylates in several respects. The gentisates required the same dosage as salicylic acid but produced no toxic reactions and controlled the manifestations of the mild or persistent disease. The important conjugates of gentisic acid that were excreted in urine are given in Table 1.

Beta Resorcylic Acid. The compound 2,4-dihydroxybenzoic or beta resorcylic acid, an isomer of gentisic acid, has low toxicity for Neubauer and Falta[17] administered single doses of 6.2 gm. to humans without serious reaction, in mice the half lethal dose was 6.6 gm. per kg. daily while dogs ingesting 150 mg. per kg. daily for several weeks had no toxic reactions (Von Oettingen[23]). Our necropsies of 2 rats that had been fed lethal doses of beta resorcylic acid found the lungs severely congested with intense vascular dilatation, toxic destruction of renal proximal convoluted tubules with severe congestion and small hemorrhagic areas in the pyramids but little inflammatory reaction except the heart valve cushions of one rat were slightly edematous.

We treated 7 patients who had rheumatic fever, 3 with pericarditis, high fever, and sedimentation rates above 100 mm. in 1 hour and 5 who had acute rheumatoid arthritis without destructive joint changes but signs of carditis, and 2 with temperatures of 103° F. and blood sedimentation rates above 100 mm. in 1 hour. Our experience with a larger group of patients prompted us to compare the action of beta resorcylic acid in rheumatic fever with the same in acute rheumatoid arthritis. The division of patients into groups according to whether the blood sedimentation rates were above or below 100 mm. in 1 hour was arbitrary but suppression of rheumatic or arthritic manifestations was found to be related to the severity of the disease.

Beta resorcylic acid was administered for 2 weeks to 3 months in 1 gm. doses every 3 hours and 6 gm. each day. The 4 patients who had rheumatic fever and blood sedimentation rates less than 100 mm. in 1 hour had symptomatic relief in 3 to 10 days with temperatures and heart rates normal in 18 to 24 days and blood sedimentation rates in an average of 26 days. The 3 patients who had rheumatic fever with pericarditis, blood sedimentation rates above 100 mm. in 1 hour and temperatures up to 103° F. had slow, limited suppression of disease manifestations, elevated temperatures and blood sedimentation rates falling but not to normal levels and heart rates and murmurs remained unchanged for 3 weeks when the drug was discontinued. One patient developed severe diarrhea.

Protocatechuic Acid. By treating patients who had rheumatic fever with 3,4-dihydroxy benzoic or protocatechuic acid, another isomer of gentisic acid, we measured the antirheumatic activity and metabolism of a compound that forms a quinone but not a chelate ring. Compounds that suppress rheumatic fever manifestations do so within 7 days of therapy so failure within such period was reasonable evidence of inactivity. We were first to administer protocatechuic acid to human subjects in quantity or for prolonged time which prompted caution. It had been given in 2 doses of 1 gm. each to febrile patients (Giacosa[7]) causing headache and a single dose of 4 gm. caused no increase in reducing power of either alkaptonuric or normal urine (Neubauer and Falta[17]). Single doses of 0.3 gm. per kg. of body weight given to rats did not produce toxic manifestations.

A purified protocatechuic acid was administered in 1 gm. doses at 3-hou. intervals and 6 gm. each day. In 3 patients who had recurrent rheumatic fever with tachycardia, fever, migrating polyarthritis, cardiac valvular disease and elevated blood sedimentation rates the results were the same. There was elevation of temperatures and heart rates,

increased rheumatic pains and general discomfort. The pre-treatment individual blood sedimentation rates of 88, 87, and 36 after 7 days of therapy were 117, 104, and 38. The 2 children became drowsy, inactive physically, mentally depressed and complained of headache.

2,3-Dihydroxy Benzoic Acid (Pyrocatechuic Acid). The compound 2,3-dihydroxy benzoic acid, an isomer of gentisic acid, was synthesized with a purity of 99.5% as determined by titration with standard sodium hydroxide solution using a Beckman pH Meter.

Case Reports. CASE 1. D.S., a woman, aged 23, had had several attacks of rheumatic fever. She had been ill one week before being seen with migratory polyarthritis, weakness, dyspnea, and sharp pain in her left chest. A pleural friction rub was heard over the base of her right lung also harsh systolic and presystolic rumbling murmurs over the apex of the heart that were transmitted into the left axilla. Her blood sedimentation rate was 130 mm. in 1 hour. The temperature was 102° F. and heart rate 110 a minute for 3 days before administration of 2,3-dihydroxy benzoic acid in 0.66 gm. doses every 3 hours and 4 gm. each day. Within the first 24 hours of therapy the temperature lowered and after 5 days became and remained normal with corresponding decline in the heart rate. After 48 hours of therapy there was striking improvement in color of her skin, pain was relieved, appetite normal, heart tones improved, and the apical heart murmurs diminished. After 3 weeks of therapy the blood sedimentation rate was 115 mm. in 1 hour.

CASE 2. G.F., a boy, aged 12, had had rheumatic fever a year before. A recent sore throat had been followed by weakness, migratory polyarthritis and loss of appetite. His temperature was 103° F., heart rate 120, and a loud systolic murmur heard over the apex of the heart was transmitted into the left axilla. The blood sedimentation rate was 58 mm. in 1 hour. He was given 5 gm. of 2,3-dihydroxy benzoic acid each day in 1 gm. doses at 3-hour intervals. His temperature dropped to and remained normal after 24 hours of therapy, as did the heart rate and there was complete symptomatic relief after 3 days of therapy. The blood sedimentation rate was 25 mm. in 1 hour after 4 days and 15 mm. after 10 days of therapy.

CASE 3. V.C., a boy, aged 15, had weakness, headache, pronounced dyspnea at rest, and a sharp stabbing pain in the lower anterior chest. His temperature was 102.8° F., heart rate 120 beats a minute, and a harsh systolic murmur was heard over the apex of the heart. He had been given aspirin 4 gm. and Achromycin 1000 mg. in divided doses each day for 4 days without relief. The initial blood sedimentation rate was 90 mm. in 1 hour. For 4 days his temperature averaged 102° F. and heart rate 120 beats a minute. He was administered 2,3-dihydroxy benzoic acid in 1 gm. doses at 3-hour intervals and 5 times each day. The temperature dropped to normal after 36 hours of therapy and remained so after the fourth day with corresponding decrease in the heart rate and disappearance of his pleural pain and effusion. He was greatly improved symptomatically after 48 hours of therapy and left the hospital free of symptoms after 11 days when the blood sedimentation rate was 25 mm. in 1 hour.

CASE 4. R.G. was a boy, aged 8. This was his second attack of rheumatic fever with migratory polyarthritis, weakness, erythema marginatum and fever of 100.4° F. The heart was enlarged, rate 100 and a systolic murmur heard over the heart's apex that was transmitted into the left axilla. The blood sedimentation rate was 92 mm. in 1 hour. He was administered pyrocatechuic acid in 0.66 gm. doses every 4 hours and 4 times each day which was increased after 3 days to 1 gm. every 3 hours for 5 times each day. After 24 hours of therapy the skin was clear and of good color, temperature normal and the joint pains were relieved. At the end of 48 hours the heart rate was 84 with sinus arrhythmia present and the apical systolic murmur was diminished. After 12 days of therapy he appeared and felt normal. The heart rate was 80 beats per minute, blood sedimentation rate 17 mm. in 1 hour and the systolic heart murmur much less audible.

The therapeutic dosage of 2,3-dihydroxy benzoic acid was 25 to 50% less than for salicylic acid. There was no toxic reaction. The compound was administered to severely ill patients but temperatures that ranged from 102° to 104° F. were normal after 1 to 5 days, heart rates after 3 to 5 days and blood sedimentation rates in 3 patients after 12 days of therapy. In 1 patient the blood sedimentation rate remained elevated after 3 weeks of therapy although all signs and symptoms of rheumatic fever were absent. After 1 or 2 days of therapy all patients had striking improvement in the color of their skin, appetite, and general sense of well being.

Gamma Resorcylic Acid. The gentisic acid isomer 2,6-dihydroxy benzoic or gamma resorcylic acid was first used for treating rheumatic fever (Reid, Watson, Cochrane and Sproul[19]) in 1951. It was reasoned that

TABLE 1.—THE DAILY URINARY EXCRETION OF PHENOLIC COMPOUNDS AND 17-KETOSTEROIDS

Patient	Daily Dose (gm.)	No. of Days	Av. Daily Drug Excretion	Average Daily Excretion of Sulfate Sulfur in mg.			Av. Daily Glucuronic Acid (mg.)	Av. Daily 17-ketosteroids* (mg.)
				Total	Inorg.	Ester		
SODIUM GENTISATE								
C.W.	0	6	———	448	404	44	296	
×	8.0	4	64.0%	437	279	158	798	
S.T.	0	4	———	336	308	28	89	
×	6.0	9	69.8%	326	234	92	152	
E.B.	0	5	———	385	372	13	165	
×	6.0	13	45.2%	308	194	114	334	
BETA RESORCYLIC ACID								
W.N.	0	2	———	430	412	18	30	3.1
×	4.5	13	75.8%	426	399	27	257	4.0
M.S.	0	2	———	167	161	6	32	2.7
×	4.5	12	57.9%	209	196	13	271	2.3
S.M.	0	2	———	251	324	17	56	6.0
×	7.0	16	42.7%	253	226	27	193	9.2
PROTOCATECHUIC ACID								
P.B.	0	3	———	451	428	23	69	1.9
×	5.33	8	22.1%	401	199	202	659	1.1
D.N.	0	3	———	320	285	35	49	7.4
×	6.00	6	24.2%	267	98	169	532	6.6
M.H.	0	3	———	297	243	54	67	5.2
×	6.00	7	34.9%	469	194	275	485	6.4
2,3,-DIHYDROXY BENZOIC ACID								
D.S.	0	3	———	611	555	56	162	8.6
×	4 gm.	22	———	589	596	83	146	8.2
G.F.	0	2		670	620	50	256	5.7
×	5 gm.	4		521	319	202	240	4.9
V.C.	0	4		2202	2062	140	667	17.1
×	4 gm.	10		957	835	122	193	7.3
GAMMA RESORCYLIC ACID								
J.F.	0	3		337	320	17	172	2.5
×	1.0	6		406	356	50	131	2.4
M.A.	0	5		380	340	40	18	7.1
×	1.0	5		404	360	44	36	6.4
L.D.	0	3		540	521	19	78	5.9
×	1.0	11		295	278	17	56	2.4
C.H.	0	3		553	507	46	72	11.2
×	1.0	8		481	434	47	133	7.4

			Severity of Disease						
Phloroglucinol Carboxylic Acid									
D.W.	0	2	++		824	766	58	251	—
×	2.0	3	++	25.0%	612	556	56	211	—
×	4.0	3	++	22.2%	555	528	27	172	—
×	6.0	7	++	19.6%	431	378	63	162	—
K.P.	0	2	+++	———	300	272	28	41	—
×	1.0	4	+++	11.4%	290	263	27	98	—
L.F.	0	4	++++	———	499	473	26	317	—
×	3.0	4	++++	9.7%	499	417	82	125	
S.B.	0	4	+	———	301	273	28	119	—
×	1.3	3	+	53.0%	377	351	26	81	—
M.H.	0	5	+	———	523	506	17	1390	4.7
×	1.3	13	+	———	370	327	43	157	5.4
S.C.	0	3	+	———	345	333	12	357	0.8
×	0.6	15	+	———	276	257	19	94	0.4
T.P.	0	3	+	———	336	308	28	146	1.2
×	1.3	7	+	———	354	332	22	115	1.8
J.P.	0	2	+	———	150	142	8	22	0.9
×	1.3	21	+	———	249	230	19	17	1.1
W.P.	0	2	+	———	430	402	28	134	6.4
×	1.3	20	+	———	650	540	65	166	8.4
2,3,6-Trihydroxy Benzoic Acid									
G.F.	0	6			449	416	33	169	6.8
×	1.0	10			315	245	70	136	4.5
D.P.	0	3			496	477	19	173	6.4
×	1.0	12			546	491	55	248	3.0
R.G.	0	3			480	459	21	59	2.7
×	1.0	21			370	246	121	128	2.2
I.I.	0	1			350	339	11	56	8.5
×	1.5	8			342	266	76	209	5.0
W.K.	0	4			316	292	24	119	4.7
×	1.0	12			355	293	60	26	3.0
R.M.	0	5			552	515	37	68	9.1
×	1.0–1.5	17			278	236	42	102	5.0

* Averages of 3 days urines with values in terms of dehydroisoandrosterone acetate.

the double chelate ring would enhance antirheumatic activity and the compound was found to be much more potent than salicylic acid. The action of gamma resorcylic acid was thought to resemble that of ACTH and cortisone in suppressing acute inflammatory reactions induced in animals by chemical irritants and in delaying wound healing. The side reactions were emotional instability, mental confusion, dry tongue and puffiness of face, acne, increased hair growth, and diminished glucose tolerance suggesting a Cushing's Syndrome.

Our gamma resorcylic acid was synthesized (Kreuchunas[12]) to a purity of 94.2% with 5.8% water as determined by titration with standard sodium hydroxide solution using a Beckman pH meter. The amounts given to patients were the same as used by Reid but no toxic reactions were observed.

Case Reports. CASE 1. A woman, M.A., aged 26, had an attack of rheumatic fever in August, 1954, with mild symptoms continuing to February, 1955, when occurred sharp anterior chest pain, dyspnea, migratory polyarthritis, and fever. A rough systolic murmur was heard over the apex of her heart that was transmitted into the left axilla. The temperature varied from normal to 100.6° F., heart rate averaged 90 beats a minute and blood sedimentation rate was 111 mm. in one hour. She was administered gamma resorcylic acid, 0.2 gm. at 3-hour intervals and 1 gm. each day. There was symptomatic relief within 24 hours and within 48 hours she was symptom free, the heart rate 72, apical systolic murmur less audible and with a higher pitched quality, and the temperature normal. The blood sedimentation rate dropped from 111 to 74 mm. in one hour on the tenth day and to 35 mm. in one hour at the end of 2 weeks when gamma resorcylic acid therapy was discontinued.

CASE 2. A woman, C.H., aged 57, had an acute respiratory infection followed by weakness, dyspnea, migratory polyarthritis, and severe precordial pain radiating to the left shoulder. The heart was enlarged to both right and left, its rate 110 beats a minute, and a rough pericardial rub was heard over the base of the heart and a low rumbling diastolic murmur over the apex which was transmitted into the left axilla. The temperature was 101° F. and blood sedimentation rate 91 mm. in one hour. She was given 0.2 gm. of gamma resorcylic acid at 3-hour intervals and 1 gm. each day. After 24 hours of therapy the chest and arthritic pains decreased, temperature was normal and after 48 hours pain was relieved, heart rate 84, and pericardial rub absent. The temperature rose to 100° F. for 24 hours on the fifth day of therapy after which it remained normal. The pretherapy blood sedimentation rate of 91 mm. dropped to 78 mm. in 1 hour on the tenth day of therapy and to 25 mm. at the end of 3 weeks.

CASE 3. A boy, J.F., aged 7, had had rheumatic fever 1 year before and was confined to bed for three months. Following an acute sore throat the present illness started as migratory polyarthritis with fever 102° F. and heart rate 128 beats a minute. A harsh systolic murmur was heard over the apex of the heart which was transmitted into the left axilla. He was given 0.33 gm. of gamma resorcylic acid every 8 hours which was increased to 0.6 gm. every 6 hours after 3 days of therapy. After 24 hours of therapy the heart rate decreased from 100 to 72 beats a minute, temperature to normal, and pain was relieved. There was a mild recurrence of symptoms with increase in the heart rate and fever on the fifth day of therapy with all returning to normal after a few hours. On the third day of therapy the intensity of the apical systolic heart murmur decreased, sinus arrhythmia appeared and his general condition improved. The initial blood sedimentation rate of 102 dropped to 39 mm. in 1 hour on the tenth day of therapy.

CASE 4. A boy, L.D., aged 6, was acutely ill with migratory polyarthritis, temperature 100.6° F., heart rate 110 beats a minute with a harsh systolic murmur heard over the heart apex transmitted into the left axilla. He had been treated with aspirin for 1 week before coming to the hospital. He was administered 0.33 gm. of gamma resorcylic acid every 8 hours. After 24 hours of therapy he showed symptomatic improvement and after 3 days the temperature was normal, heart rate 80 with sinus arrhythmia present and the systolic heart murmur decreased in intensity. All symptoms were relieved at the end of 48 hours of therapy and the initial blood sedimentation rate of 49 was 17 mm. in 1 hour on the twelfth day of therapy.

Many manifestations of rheumatic fever were uniformly suppressed within 1 or 2 days of gamma resorcylic acid therapy but especially pain and other arthritic manifestations. The temperatures and heart rates were normal after 1 to 3 days of therapy and the blood sedimentation rates fell rapidly. The effect of gamma resorcylic acid was generally good on symptoms, signs of carditis, fever, and heart rate and the compound at least 5 times more potent than salicylic or gentisic acids. Patients did not experience the early

sense of well being or striking improvement in appetite and skin color that had been observed with gentisic acid.

Phloroglucinol Carboxylic Acid. The significance of a third hydroxy group in the 4 position of a double chelating phenolic compound was investigated in 23 patients, 12 having rheumatic fever. The compound used was 2,4,6-trihydroxy benzoic or phloroglucinol carboxylic acid. Patients were administered 1 gm. to 6 gm. of the compound each day for periods of 7 days to 3 months, most receiving 1 gm. to 1.33 gm. of the compound in divided doses each day for 10 to 12 weeks. There were no toxic reactions.

Some manifestations of rheumatic fever were suppressed within 2 or 3 days of therapy, temperatures were normal in 6 to 10 days, blood sedimentation rates within 4 weeks with some in 7 to 14 days. When therapy was started a few days after onset of the disease there was unusual restoration of normal heart findings. It seemed possible for this compound to prevent heart damage if used early in rheumatic fever. The antirheumatic potency of phloroglucinol carboxylic acid was 6 to 8 times greater than that of salicylic acid.

2,3,6-Trihydroxy Benzoic Acid. The compound 2,3-dihydroxy benzoic acid had outstanding antirheumatic activity and 2,6-dihydroxy benzoic acid had many but not all of the same therapeutic qualities but was at least 5 times more potent. We combined these therapeutic features by synthesizing the compound 2,3,6-trihydroxy benzoic acid (Kreuchunas[13]) which was administered to patients in 0.2 gm. doses at 3-hour intervals 5 times each day but decreased to 4 times or increased to 0.3 gm. at 3-hour intervals 5 times a day under special circumstances. The usual effective amount was 1.0 gm. in divided doses each day. There were no toxic reactions.

Case Reports. CASE 1. G.F., a boy, aged 11, one week after hospitalization for a severe leg burn his temperature rose suddenly to 104° F. with the development of severe dyspnea, cough, chest and migratory arthritic pains, and rapid forceful heart action. A rough systolic murmur was heard over the apex of his heart transmitted into the left axilla. The compound 2,3,6-trihydroxy benzoic acid was administered in 0.2 gm. doses at 3-hour intervals and 5 times each day .

His temperature was normal at the end of 24 hours of therapy except for a daily rise to 99° F. for 7 more days. The heart rate was 120 but dropped to 84 after 48 hours of therapy and after 72 hours to 72 with diminished intensity of the apical systolic murmur and return of sinus arrhythmia. On the eleventh day of therapy the murmur was not audible. The arthritic pains were relieved after 24 hours of therapy and after 48 hours he felt normal except for the symptoms caused by the leg burn. The preliminary blood sedimentation rate of 104 mm. in one hour dropped to 69 mm. in one hour after 6 days and to normal after 2 weeks of therapy.

CASE 2. W.K., a boy, aged 6, had had previous attacks of rheumatic fever and when seen was acutely ill, listless, mentally dull with painful swollen red joints. The heart action was forceful, rate 140 and a harsh systolic murmur was heard over the apex of the heart that was transmitted into the left axilla. The compound 2,3,6-trihydroxy benzoic acid was administered in 0.2 gm. doses at 3-hour intervals and 5 times each day for 5 days when it was reduced to 0.2 gm. at 3-hour intervals 4 times a day. On the second day of therapy he was cheerful, mentally alert, free of arthritic manifestations, heart rate was 100 and the heart murmur diminished. After 4 days of therapy sinus arrhythmia appeared and he felt well. On the 6th day the heart rate was 80 and on the 7th had decreased to 74 with the heart murmur greatly diminished. After 10 days of therapy the heart sounded normal. The temperature remained normal after 3 days of therapy. The pretherapy blood sedimentation rate of 70 mm. in one hour was 33 mm. in one hour on the 5th day and 12 mm. in one hour on the 10th day of therapy.

CASE 3. R.M., a girl, aged 17, had a history of rheumatic fever and rheumatic heart disease. She was acutely dyspneic and orthopneic, nauseated, weak, had multiple swollen, painful, red joints, appeared flushed, toxic, and coughed frequently. The heart was enlarged, its rate 120 with a pericardial friction rub heard over the base and harsh systolic and presystolic rumbling murmurs over the apex of the heart that were transmitted into the left axilla. The compound 2,3,6-trihydroxy benzoic acid was administered in 0.2 gm. doses at 3-hour intervals for 5 times each day and after 8 days increased to 0.3 gm. every 3 hours 5 times each day. She had symptomatic improvement at the end of 36 hours of therapy and on the 4th day her breathing was normal, arthritis relieved, heart less active and murmurs diminished. The heart rate gradually slowed and at the end of 10 days was 72 and the heart murmurs were greatly diminished. The pericardial friction rub was absent after 1 week of therapy. The temperature of 103 to 104° F. dropped to normal

on the third day of therapy, rose to 101° F. but became and remained normal on the fifth day. The blood sedimentation rate was 59 mm. in 1 hour but rose to 100 mm. in 1 hour 8 days later when the compound was increased. Thereafter it gradually declined and was normal after 4 weeks of therapy.

CASE 4. R.G., a boy, aged 7, whose illness started mildly as fever, migratory joint pains, nose bleeds and anorexia. He looked ill with his right knee swollen, red and painful, heart action forceful, heart size normal and without murmurs. The arthritic symptoms increased, dyspnea developed, the heart rate rose to 120, a pericardial rub appeared over the base, and a rough systolic murmur over the apex of the heart. The compound 2,3,6-trihydroxy benzoic acid was administered in 0.2 gm. doses every 3 hours and 5 times each day. The dyspnea and arthritic pains were relieved in 24 hours and after 4 days his temperature dropped from 104° F. to normal, the heart rate from 120 to 92 and the heart murmur and friction rub were less audible. The heart sounds became distant, temperature and heart rate increased and serial roentgenograms of his chest revealed increased size of the heart shadow. Meticorten 5 mg. which was administered every 6 hours was rapidly reduced and stopped after 10 days. This arrested the rapidly developing pericardial effusion. The 2,3,6-trihydroxy benzoic acid was continued during and after the use of Meticorten. After discontinuing Meticorten he improved rapidly and at the end of 1 month felt well, the heart size was normal, heart rate 84, pericardial rub absent and the apical systolic heart murmur was greatly diminished. The temperature was normal on the 4th day of 2,3,6-trihydroxy benzoic acid therapy but rose on the 7th day with the development of the pericardial effusion but became and remained normal after 13 days of therapy. The blood sedimentation rate of 125 mm. in 1 hour declined after 12 days of therapy to 77 mm. in 1 hour but remained at 61 mm. in 1 hour after 4 weeks when he was symptomatically well and signs of carditis were absent. He had malignant rheumatic fever for which we chose not to increase the 2,3,6-trihydroxy benzoic acid but use temporarily the corticosteroid.

CASE 5. L.L., a man, aged 61, had a history of previous rheumatic fever. His present illness started with severe dyspnea, weakness, and migratory polyarthritis. The heart size was normal, rate 100 with a harsh systolic murmur heard over the apex of the heart that was transmitted into the left axilla. Roentgenograms of his chest revealed large hilar shadows and bilateral pneumonitis. The compound 2,3,6-trihydroxy benzoic acid was administered in 0.3 gm. doses every 3 hours for 5 times each day. The pretreatment temperature of 100° F. was normal after 24 hours of therapy. After 48 hours therapy he was symptom-free and the heart rate 88 which dropped to 72 on the 12th day of therapy. The earlier signs of pneumonitis were not found on chest roentgenograms that were taken on his tenth day of therapy. The blood sedimentation rate of 84 mm. in 1 hour fell rapidly to 45 mm. in 1 hour after 6 days and to 18 mm. in 1 hour at the end of his second week of therapy.

CASE 6. D.P., a boy, aged 10, had low abdominal, inguinal and migratory joint pains, weakness, nausea, and daily elevation of temperature to 99.6° F. His heart was of normal size and a rough systolic murmur was heard over the apex of the heart that was transmitted into the left axilla. The con ound 2,3,6-trihydroxy benzoic acid was administered in 0.2 gm. doses at 3-hour intervals and 5 times each day. At the end of 24 hours' therapy he felt well and after 5 days his heart rate was normal, sinus arrhythmia present and the apical systolic murmur less audible. The temperature became and remained normal after 2 days of therapy. The pretreatment blood sedimentation rate of 86 mm. in 1 hour dropped to 52 after 3 days and to 34 after 11 days of therapy.

The compound 2,3,6-trihydroxy benzoic acid was superior to all other phenols in our series being free of side reactions, highly effective in small doses and suppressed manifestations of severe rheumatic fever. Most symptoms were relieved in 1 or 2 days of therapy, temperatures became normal in 1 to 5 days even in severe forms of the disease. The heart rates returned to normal in an average of 11 days of therapy but varied from 3 to 30 days according to the severity and complications of the disease. When pericarditis was absent the heart rate was normal in an average of 8 days. The appearance of all patients improved along with a sense of well-being within the first 48 hours of therapy. In 5 patients the blood sedimentation rates were normal within the first 12 days of therapy but in Case 4 remained elevated after 30 days but he had the malignant form of the disease.

EFFECT ON ABSOLUTE EOSINOPHIL CELL COUNT AND WHITE BLOOD CELLS. A modified Thorn test with consecutive

hourly absolute eosinophil cell counts was done. Patients were administered 30 mg. of beta resorcylic acid for each kilogram of body weight. The absolute eosinophil cell counts of normal subjects and patients with rheumatic fever and rheumatoid arthritis decreased more than 50%, the drop occurring within 1 to 4 hours after ingesting the drug. With the suppression of rheumatic fever manifestations there were decreased polymorphonuclear and increased lymphocyte cell counts.

To 2 normal subjects and 3 patients we administered 30 mg. of protocatechuic acid for each kilogram of body weight. No significant difference was found in the eosinophil cell counts of normal controls and patients administered the compound.

After normal counts had been determined 5 patients were administered 0.15 gm. of 2,3-dihydroxy benzoic acid for each kilogram of body weight. There was a 65 to 85% reduction of eosinophil cells in 2 or 3 hours after drug was administered with counts rising after 5 hours. The lymphopenia produced by the antirheumatic corticosteroids is thought to be due to lysis of fixed lymphoid tissue. Although phenols produce significant eosinopenia contrariwise they increase circulating lymphocytes.

After determining normal counts, patients were administered 0.04 gm. of gamma resorcylic acid for every kilogram of body weight. There was a 60 to 75% reduction in the eosinophil cell counts at the end of 1 to 3 hours with slight elevation at the end of 4 hours.

We found a shift to the left in white blood cell counts an index of response to therapy. This shift did not always coincide with a decline in blood sedimentation rates which are notoriously unreliable. Using the ratio of neutrophils to lymphocytes, the white blood cell counts prior to therapy averaged 2.9 and changed to 1.44 when therapy was discontinued. A significant rise in lymphocyte cells always occurred with suppression of rheumatic fever manifestations.

Normal eosinophil cell counts were determined and counts repeated after giving patients 0.033 gm. of phloroglucinol carboxylic acid per kilogram of body weight. The eosinophil cell counts declined but never by more than 40% of the preliminary levels. Frequent white blood cell counts were made on 10 patients who were being treated with phloroglucinol carboxylic acid and 8 patients had a striking increase in their absolute lymphocyte counts but not in 2 who had malignant rheumatic fever, one dying although he was also treated with cortisone.

Absolute eosinophil counts were made at 4 consecutive hourly intervals on 5 patients who had ingested 0.066 gm. of 2,3,6-trihydroxy benzoic acid for each kilogram of body weight. The maximum fall in eosinophil cells was 44%. This compound always caused pronounced elevation of lymphocyte counts.

THE URINARY EXCRETION OF PHENOLIC COMPOUNDS. In Table 1 are the urinary excretion analyses of 3 patients who had rheumatic fever and were administered 6 gm. of beta resorcylic acid each day. Each figure represents the average for 3 days' urinary output. The excretion of 17-ketosteroids was not changed and the excretion of beta resorcylic acid was largest by 2 children. There was sharp increase in urine glucuronic acid and a correlation between urinary beta resorcylic and glucuronic acid levels but there was no change in output of ethereal sulfate.

The urine analyses of 3 patients who were ingesting 6 gm. of protocatechuic acid each day are in Table 1. The com-

pound did not change the urinary excretion of 17-ketosteroids.

A large amount of protocatechuic acid was excreted in a bound or modified form. Ethereal sulfate and glucuronic acid conjugates excretion increased sharply and must account for most of the bound drug, an excretion pattern that resembled that of the ethanolamide of gentisic acid (Clarke and Mosher[2]). Both compounds lack the ortho hydroxyl group that generally increases excretion of ester sulfates but it may be the result of a complete breakdown of protocatechuic acid in the body or by partial decarboxylation to form catechol which has been reported (Preusse[18]). We did not analyze urines for catechol or decomposition products.

A total excreted determination for 2, 3-dihydroxy benzoic acid was difficult to obtain due to its labile nature. The usual detoxication and urinary excretion of phenols as conjugates makes the metabolism of 2, 3-dihydroxy benzoic acid unusually important. The urinary excretion figures for this compound in Table 1 demonstrate decreased urinary output of sulfur and glucuronides. The decrease for total sulfur is pronounced but not for the ester. There was significant decrease in the urinary excretion of glucuronides but only a suggestive decrease in the excretion of 17-ketosteroids.

Reid *et al.*[19] used a colorimetric method of determination and reported urinary excretion of gamma resorcylic acid equaling 63 to 73% of the administered drug. We measured the urinary excretion of sulfur and glucuronic acid conjugates of gamma resorcylic acid and also 17-ketosteroids which are in Table 1. The urines had reduced to slightly elevated sulfate-sulfur with glucuronides decreased or little changed, being elevated in 1 patient who had severe pericarditis. The failure of gamma resorcylic acid to generate detoxication mechanisms is unusual and even the patient with severe carditis and increased urinary glucuronides had decreased urinary sulfur. The decrease in urinary excretion of sulfur is more significant than for glucuronides with phenolic antirheumatic activity.

The urine analyses for 7 of 9 patients who were treated for rheumatic fever with phloroglucinol carboxylic acid are given in Table 1 and have less than normal glucuronic acid with the decrease paralleling the amount of compound that was administered so glucuronic acid metabolism was effected directly by some process other than detoxication.

The urinary excretion of sulfates with administration of phloroglucinol carboxylic acid decreased in 5 of 9 patients and in only one was the change in combined sulfate of the same magnitude as the corresponding change in inorganic sulfate. Phloroglucinol carboxylic acid effects sulfur metabolism in the human body in a different manner than detoxication or the formation of combined sulfates.

The average daily urinary excretion of phloroglucinol carboxylic acid was low and varied according to the severity of the rheumatic fever. The highest outputs were from patients who had mild attacks of the disease.

The urinary excretion characteristics of 2,3,6-trihydroxy benzoic acid are in Table 1 with the significant metabolic determinations being decreased urinary excretion of sulfate sulfur in 4 of 6 patients, decreased 17-ketosteroids in all with glucuronides decreased in 2 of 6 patients. The excretion of sulfate sulfur was not significantly increased in any patient, 17-ketosteroids were consistently reduced and glucuronic acid excretion was elevated significantly only in patients R.G., L.L., and R.M.

who had at least submalignant rheumatic fever.

Discussion. The therapeutic dominance of salicylic acid for rheumatic fever clearly indicates a vital relationship between the compound's simple chemical structure and the biochemical distortions produced by the disease. There is reason for believing that the therapeutic action of salicylic acid is due to its metabolites (Hawk, Oser and Summerson[9] and Clarke, Mosher and Clarke[3]). The monophenol salicylic acid produces several undesirable toxic reactions but its metabolite gentisic acid, a diphenol, is nontoxic and superior therapeutically. A chelate ring is essential for a phenolic compound to have antirheumatic properties (Clarke, Mosher and Clarke[3] and Tormey and Barnhurst[22]) but the importance of second or third hydroxyl groups and their position on the benzene ring has had limited investigation.

Beta resorcylic acid differs from gentisic acid in the position of the second hydroxyl group, the latter being able to form a reversible quinone-hydroquinone system. Salicylic acid (Ivanovics[10]) and beta resorcylic acid (Moore[16]) are antimetabolites for certain organi ns and differences in their toxicity and ability to suppress the manifestations of rheumatic fever or rheumatoid arthritis could in part be due to their action as metabolic antagonists. Beta resorcylic acid suppressed the manifestations of rheumatic fever less effectively than did gentisic acid, its antiarthritic properties being greater than its influence on the manifestations of carditis.

The respiration of selected animal tissues is accelerated by low concentrations of compounds having labile hydrogen atoms which can be readily and reversibly converted to quinones with oxygen carrying ability. Beta resorcylic acid has an inhibiting action on oxygen consumption (Monguio[15]). The greater effectiveness of gentisic acid in rheumatic carditis and beta resorcylic acid in rheumatoid arthritis could be due to the differences in the oxygen requirements of different connective tissues.

Protocatechuic acid forms a quinone but not a chelate ring and does not suppress the manifestations of rheumatic fever. Patients who have ingested protocatechuic acid excrete dark urines due to a quinone of protocatechuic acid for homogentisic acid was eliminated by negative chemiluminescence tests. Chelation does not account entirely for the antirheumatic activity of some diphenolic compounds. Therefore, the position of second or third hydroxyl groups on the benzene ring is of greatest importance. The ability of gamma resorcylic acid to suppress rheumatic fever manifestations without prompting detoxifying mechanisms indicates that chemical stresses induced by rheumatic fever are naturally fortified by the double chelating structure. This compound was completely utilized or unusually changed in some manner with a saving action suggested by the significant decrease in urinary excretion of 17-ketosteroids.

The second hydroxyl group in the 3 position of 2,3-dihydroxy benzoic acid improved antirheumatic activity without prompting detoxication mechanisms. Unlike other phenols the excretion of phenolic conjugates of sulfur and glucuronides were decreased in urines passed by patients who had ingested 2,3-dihydroxy benzoic acid. Other conjugated metabolites if they had been present would have been detected unless the compound had undergone change to a different form. Perhaps 2,3-dihydroxy benzoic acid is a natural or completely utilizable compound that needs no detoxication and

acts to normalize the chemical stresses induced by rheumatic fever.

The compound phloroglucinol carboxylic acid has had little attention but what is known emphasizes its unusual characteristics. It increases capillary resistance by acting on adrenalin (Salva, Neumann and Lavollay[20]) and combines reversibly in aqueous solution with HCO_3^- in a reaction that is unique. Near its equilibrium point the velocities of the forward and backward reactions are unequal as checked by electrometric titrations (Bauer and Giger[1]). The decrease in urinary excretion of sulfur and glucuronic acid by patients who had ingested phloroglucinol carboxylic acid is unusual for excepting 2,3-dihydroxy benzoic acid and gamma resorcylic acid phenolic compounds have increased urinary output of one or both of these detoxifying agents.

The low excretion rate of this compound suggests it is readily metabolized by the human body. Its labile nature in terms of tendency to decarboxylate under the influence of heat in aqueous solutions may account in part for the low daily excretion records.

The compound 2,3,6-trihydroxy benzoic acid had lower toxicity, acted more promptly to suppress manifestations of rheumatic fever and lower elevated blood sedimentation rates than did all other phenolic compounds. Like other double chelating phenols in this series it usually decreased urinary excretion of sulfur and glucuronic acid conjugates except in patients who had malignant or submalignant rheumatic fever. These metabolic findings suggest a normalizing or saving action on special connective tissue components. The compound 2,3,6-trihydroxy benzoic acid produced significant and consistant reduction in the urinary excretion of 17-ketosteroids which lends support to it having a saving action in rheumatic fever.

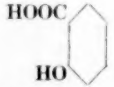
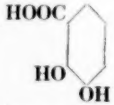
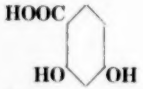
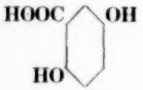
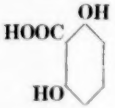
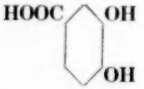
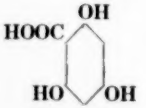
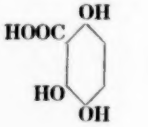
In some unknown way, but probably precipitated by a group A hemolytic streptococcus infection, rheumatic fever attacks connective tissue and particularly mucoid or ground substance. The composition of ground substance varies according to the tissues function but consists in large part of polysaccharides with glucuronic acid and chondroitin sulfate present as long chain polymers. The exudative phase of rheumatic fever disrupts the collagen-muco-polysaccharide complexes as might occur with depolymerization. This phenomenon has been related to actions by hyaluronidase. The *in vitro* actions of hyaluronidase are inhibited by large concentrations of salicylates (Dorfman, Reimer and Ott[4]), by smaller concentrations of gentisic acid (Von Oettingen[23]) and by the quinones of gentisic acid (Glick, Bieter and Wright[8]).

The pathogenesis of rheumatic fever is unknown and action of drugs determined in part by the functional status of connective tissue cells. The important variations in clinical response and differences in metabolic patterns summarized in Table 2, when interpreted according to accepted principles of detoxication, suggest the mechanism of phenolic antirheumatic activity.

This data compares chemical structure and metabolites with antirheumatic properties. It supports the importance of chelation and demonstrates that potency is greatly increased by a second hydroxyl group in the 6 position. The toxicity of a phenol is reduced by a second hydroxy group but least when in the 4,6 and most in the 3,5 positions. The toxicity of phenolic compounds with a second hydroxyl group in the 4 or 6 position is abolished by a third hydroxyl group. The high-

TABLE 2.—COMPARISON OF CLINICAL RESPONSE AND METABOLISM OF MONO, DI AND TRIPHENOLIC COMPOUNDS IN RHEUMATIC FEVER

TABLE 2.—COMPARISON OF CLINICAL RESPONSE AND METABOLISM OF MONO, DI AND TRIPHENOLIC COMPOUNDS IN RHEUMATIC FEVER

	Antirheumatic Potency	*Toxicity in Therapeutic Doses*	*Urinary Excretion of Conjugates*		*Urinary Excretion 17-Ketosteroids*	*Eosinopenia 50% Plus*	*Action on Circulating Lymphocytes*	*Prevention of Heart Damage with Early Use*
			Total Sulfur	*Glucuronides*				
 Salicylic Acid	1.	High	No change	Increased	No change	Yes	Increased	No
 Pyrocatechuic Acid	2.	Absent	Decreased	Decreased	Decreased	Yes	Increased	No
 Beta Resorcylic Acid	1.	Low	No change	Increased	No change	Yes	Increased	No
 Gentisic Acid	1.	Absent	Increased	Increased	—	Yes	Increased	No
 Gamma Resorcylic Acid	5.	Low	Decreased	Decreased	Decreased	Yes	Increased	No
 Protocatechuic Acid	None	High	No change	Increased	No change	No	No change	No
 Phloroglucinol Carboxylic Acid	8.	Absent	Decreased	Decreased	Decreased	No	Increased	Possible
 2,3,6-Trihydroxy Benzoic Acid	10.	Absent	Decreased	Decreased	Decreased	No	Increased	Probable

est toxicity was found in the diphenol protocatechuic acid which is not a chelating compound so the ortho position of a hydroxyl group decreases side reactions.

When unnatural or harmful compounds are ingested, the body detoxicates and excretes them commonly as conjugates of sulfur or glucuronic acid. This has been found in previous reports on phenolic compounds (Von Oettingen[23]). Of the mono- and diphenols, salicylic, beta resorcylic, and protocatechuic acids were excreted as conjugates of sulfur and glucuronic acid and gamma resorcylic acid decreased normal urinary levels of these compounds except in the malignant form of rheumatic fever. Phenolic compounds that conjugate only with glucuronic acid have maximum toxicity and lowest antirheumatic activity. The corticosteroids increase the sulfur output in urine (Kinsell, Li, Margen, Michaels and Hedges[11]). A second hydroxyl group added in the 6 position to the structure of salicylic acid greatly increased therapeutic potency with reduction in urinary excreted sulfur and glucuronic acid but a second hydroxyl group in the 3 position only slightly improved potency but also diminished sulfur and glucuronic acid excreted in urine.

Trihydroxy phloroglucinol carboxylic acid has the chemical structure of a double chelate ring and an hydroxyl group in the 4 position like beta resorcylic acid. The double chelate ring removed the mild toxicity caused by the fourth position hydroxyl group with a single chelate ring.

The smaller amounts of gamma resorcylic, pyrocatechuic, and triphenolic acids required to suppress the manifestations of rheumatic fever as compared to salicylic acid supports the role of antirheumatic metabolites. The compounds with reversible quinone hydroquinone systems manifested superior antirheumatic qualities. The most important hydroxyl group outside the 2 or 6 positions was the 3 position of pyrocatechuic acid, the only diphenol that decreased urinary excretion of sulfur and glucuronic acid conjugates. The qualities attaching to 2, 6, and 3 positions of hydroxyl groups were combined in the compound 2, 3, 6-trihydroxy benzoic acid. This new compound had maximum antirheumatic potency, was nontoxic, decreased the urinary excretion of sulfur and less so of glucuronic acid.

The decrease in urinary sulfur with ingestion of more potent phenolic compounds was generally constant but glucuronides increased some in severe or malignant rheumatic fever. The limited supply of some compounds prevented us from determining if larger dosages would produce constant metabolic changes in mild and malignant forms of the disease.

The antirheumatic actions of salicylic, gentisic, and gamma resorcylic acids have been compared with ACTH and adrenal steroids. We found the urinary excretion of 17-ketosteroids not altered by salicylic, beta resorcylic, or protocatechuic acids but decreased by pyrocatechuic acid and 3 compounds having double chelate rings.

The absolute lymphocyte count was significantly increased by all phenolic compounds having antirheumatic properties. The elevation of lymphocytes paralleled clinical improvement which is contrary to reports for adrenal antirheumatic hormones. Absolute eosinophil cell counts were not significantly decreased by triphenols which had the highest antirheumatic activity although urinary excretion of 17-ketosteroids and sulfur were decreased. The phenolic compounds and antirheumatic adrenocorticosteroids do not suppress the manifestations of rheu-

matic fever by the same process (Thorn[21]).

In triphenol antirheumatic therapy there is a quantitative relationship between the severity of the disease and the level of urinary conjugates. The triphenols are utilized by patients with rheumatic fever as natural substances not requiring and actually reducing other processes of detoxication. These compounds must serve directly in completing synthesis and polymerization of disrupted connective tissue.

The greater therapeutic activity of beta resorcylic acid in rheumatoid arthritis and of gentisic acid in rheumatic fever demonstrates that change in the position of the second hydroxyl group made each act best on the damaged connective tissue component that differentiates the 2 diseases. Such selective action strengthens belief in a direct chemical normalizing effect by phenolic compounds. This is supported by antimetabolic functions of some phenols and oxygen carrying ability of quinones present in phenols with highest antirheumatic activity. Natural antirheumatic hormones may be potentiated by blocking their destruction as in hepatitis or increasing local tissue sensitivity.

The psychologic effects of mild euphoria and improved sense of well-being that are observed with hormone therapy have been striking features with improved phenol therapy, with none of the side reactions of the hormones.

This study was necessarily limited but carefully considered observations permit the belief that triphenols and especially 2,3,6-trihydroxy benzoic acid when administered early in a first attack of rheumatic fever bring unusually rapid recovery without residual signs of heart damage.

Summary. By adopting the principle of investigating chemicals related to one manifesting therapeutic activity, we sought an improved treatment for rheumatic fever. We tested compounds related to salicylic acid or the diphenols gentisic acid, protocatechuic acid, pyrocatechuic acid, beta resorcylic acid, gamma resorcylic acid, and the triphenols phloroglucinol carboxylic and 2,3,6-trihydroxy benzoic acids.

Increased antirheumatic potency was found in phenolic compounds with double chelate rings and superior antirheumatic qualities were associated with a second or third hydroxyl group in the 3 position on the benzene ring.

The compounds that had double chelate rings or single chelate ring and hydroxyl group in the 3 position did not generate usual urinary changes associated with detoxication.

Phenolic compounds produce some changes that are associated with antirheumatic adrenal hormones but differed by producing relative increases in circulating lymphocyte cells and decreasing the urinary excretion of 17-ketosteroids.

The high antirheumatic potency of double chelating phenols supports the importance of antirheumatic metabolites in salicylic acid therapy. The compound 2,3,6-trihydroxy benzoic acid has the highest potency but is nontoxic and when used early in the first attack of rheumatic fever seemed to prevent damage to the heart.

Certain phenolic compounds have a normalizing or saving action in rheumatic fever thereby permitting their direct utilization by the body.

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SUMMARIO IN INTERLINGUA

Compositos Phenolic In Le Chimotherapia De Febre Rheumatic

Guidate per le principio del investigation de substantias chimic que es relationate a un cognoscite agente therapeutic, nos cercava meliorar le tractamento de febre rheumatic. Nos testava compositos relationate a acido salicylic, *i.e* le diphenoles acido gentisic, acido protochatechuic, acido pyrocatechuic, acido resorcylic beta, e acido resorcylic gamma e le triphenoles acido phloroglucinolcarboxylic e acido 2,3,6-trihydroxybenzoic.

Augmento del potentia antirheumatic esseva constatate in compositos phenolic con duple anulos de chelation, e qualitates antirheumatic superior esseva associate con un secunde o un tertie gruppo hydroxylic in position 3 del nucleo de benzena.

Le compositos con duple anulos de chelation o simple anulo de chelation con presentia de gruppo hydroxylic in position 3 non generava le usual alterationes urinari associate con detoxication.

Compositos phenolic produceva certe alterationes associate con antirheumatic hormones adrenal sed differeva per producer augmentos relative de lymphocytos circulante e reductiones relative del excretion urinari de 17-cetosteroides.

Le alte potentia antirheumatic de phenoles a duple chelation supporta le concepto del importantia de metabolitos antirheumatic in therapia a acido salicylic. Le composito acido 2,3,6-trihydroxybenzoic ha le plus alte potentia. Illo es nontoxic. Quando illo es usate promptemente durante le prime attaco de febre rheumatic, illo pare prevenir damnos cardiac.

Certe compositos phenolic exerce un action normalisante in febre rheumatic e permitte lor utilisation directe per le corpore.

HOST FACTORS AFFECTING GROWTH OF B-HEMOLYTIC STREPTOCOCCI IN THE HUMAN PHARYNX: A PILOT STUDY

By William W. Schottstaedt, M.D.
ASSOCIATE PROFESSOR OF MEDICINE AND PREVENTIVE MEDICINE

James H. Krause, A.B.
SENIOR MEDICAL STUDENT

David W. Foerster, A.B.
SENIOR MEDICAL STUDENT

Robert T. Dooley
SENIOR MEDICAL STUDENT

AND

Florene C. Kelly, B.S., M.S., Ph.D.
PROFESSOR AND HEAD OF THE DEPARTMENT OF MICROBIOLOGY

(From the Departments of Medicine, Preventive Medicine, and Microbiology, Oklahoma University School of Medicine, Oklahoma City, Oklahoma)

It is a common clinical observation that certain people are prone to develop upper respiratory infections, while others are not. It is also known that potential pathogens are frequently found in individuals who have no clinical illness and that local factors favoring growth are important to the development of the infectious diseases. Little is known about the factors which influence the establishment of the streptococcus in the throat or which determine its continuance there or its disappearance.

Hinkle and Plummer[3], in a study of workers at the New York Telephone Company, showed that a small segment of their population was subject to a high proportion of the illnesses, including infectious diseases. They found that the group who had frequent and prolonged illnesses were, in general, individuals who were dissatisfied with their work and experiencing difficulties in their adjustment at work and at home. They were individuals with a high degree of insecurity. On the other hand, the group who had a very low proportion of the illnesses were individuals who were well adjusted both at work and at home. This study might suggest a relationship between personal adjustment and infectious disease.

Certain local factors in the nose and nasopharynx which might affect bacterial growth have been studied. Tweedie[5] reported that the bacterial flora of the nose correlated closely with pH. Fabricant[1] studied the pH of the nasal passages and found it to be continuously variable, responding to changes in temperature, to rest or sleep, and to attacks of rhinitis. He reported a close relationship existing between nasal pH and certain emotional states occurring in his subjects[2]. Holmes and his co-workers[4] also studied the nose and found marked changes in the type and amount of secretion and in the vascularity of the nasal mucosa in association with various emotional reactions to stressful life situations. These studies demonstrate that local conditions within the nose

and throat undergo fairly rapid changes and that these changes are of a sort which might be expected to affect bacterial growth.

The present project was undertaken as a pilot study to learn whether these problems could be satisfactorily attacked so that some of the host factors determining the appearance of clinical manifestations might be clarified.

Method. The subjects for this study were 3 families chosen from the Rheumatic Fever Clinic of the Oklahoma University Medical Center. Each family had at least one child who had had rheumatic fever and several others who had not. The 3 families had 26 members, 25 of these being included in the study (one father was not available for bacteriologic observations). All 3 families lived within the city-limits of Oklahoma City and all were of the lower economic level.

Each family was visited at home 2 or 3 times a week for 8 weeks. On each visit the color of the pharynx was recorded for each member of the family, using a 3-point scale of pink, red, or injected. The amount of nasopharyngeal secretions was also estimated grossly as small, moderate or large. pH determinations were recorded using a portable pH meter. In addition, a swab of the posterior pharynx was obtained at each visit. A single investigator made all the visits in order to minimize variation in subjective evaluations of throat color and pharyngeal secretions. Twice during the study, blood was drawn from each of the 25 subjects for determination of ASO titer. Height, weight, and hemoglobin determinations were recorded for each subject.

Each family was asked to keep a diary. The investigator read this at each visit, then asked questions to explain items which were not clear. In addition, he talked to the members of the family to learn anything additional that he could. The diary emphasized the day-to-day events for each member of the family and gave details about symptoms experienced, with particular emphasis on sore throats or the common cold.

Throat swabs were obtained and brought to the laboratory in tubes containing 1 ml. thioglycolate-dextrose broth or 1 ml. tripticase-soy broth. Plates were streaked on tripticase-soy agar to which sterile blood had been added. After 24 hours' incubation, these plates were read and suspicious colonies were smeared and stained. If positive, an isolated colony was streaked on a new plate with a grouping disc and incubated 24 hours. Slants were made of these positive cultures and frozen milk cultures were obtained for subsequent studies.

In addition, local climatological data were obtained from the weather station giving temperature, precipitation, barometric pressure and wind velocity for the entire period of the study. Figures were also obtained from the Public Health Department on the reported incidence of streptococcal sore throat in the community during the study.

Results. I. SURVEY OF BACTERIOLOGIC DATA. A total of 450 cultures were obtained on 25 subjects during the 2-month period of the study. Beta-hemolytic streptococci were present in 16% of the cultures, being the predominant organism in 5%. The incidence of cultures positive for beta-hemolytic streptococci seemed to fall into 3 groups. The incidence was fairly high from the onset of the study until October 20, at which time there was an abrupt decrease. A few individuals in the 3 families continued to carry streptococci for the next 2 weeks; but all streptococci disappeared in all 3 families after the first of November. (See Table 1.)

II. CLIMATIC CHANGES. The climate during this study also fell into 3 broad periods. The first of these was from the onset of the study until the 13th of October at which time a mild cold wave reached the City. There was a period of moderate cold and rainfall between October 14 and November 1 and this was followed by a period of colder weather down to freezing temperatures. (See Table 2.)

It is apparent from these facts that changes in temperature showed a correlation opposite to that which would have been anticipated, since streptococcal sore throat and rheumatic fever generally show their high incidence during the colder weather. Changes in the weather, therefore, did not account for the decrease in incidence of cul-

tures positive for beta-hemolytic streptococci.

III. INCIDENCE IN THE COMMUNITY. Table 3 summarizes the reported incidence of streptococcal sore throats in the community in which this study was performed. Though this cannot be used as a reliable index of the prevalence of streptococci, it affords the only index available. Comparison of the curve of incidence of streptococcal sore throat in the community with positive cultures observed in these 3 families showed no correlation between the two. The incidence reported in the community as a whole was consistent, however, with climatic changes occurring during the period of study.

TABLE 1.—CULTURES POSITIVE FOR BETA-HEMOLYTIC STREPTOCOCCI

Dates	*Number of Cultures*	*Number Positive*	*% Positive*
9/20 to 10/20	252	58	23
10/20 to 11/1	116	12	10
11/1 to 11/15	86	0	0
	454	70	16

TABLE 2.—VARIATIONS IN CLIMATE DURING PERIOD OF STUDY

Date	*Maximum Temperature*	*Minimum Temperature*	*Rain*
9/10 to 10/13	80 to 100	50 to 71	Trace on 10/13
10/14 to 11/1	66 to 78	39 to 60	3.76 inches
11/2 to 11/10	46 to 61	32 to 47	1.48 inches

TABLE 3.—REPORTED INCIDENCE OF SCARLET FEVER AND STREP THROAT IN THE COMMUNITY

Month	*State*	*County*	*City*
September	252	33	21
October	225	19	19
November	354	86	70

IV. EXPOSURE TO BETA-HEMOLYTIC STREPTOCOCCI. A 19-year-old girl in Family L had had rheumatic fever but was not taking antibiotics. At no time during the study did she show beta-hemolytic streptococci in her pharyngeal cultures though she was sleeping with a sister who showed these on 4 occasions. Two younger siblings who also had had rheumatic fever and were taking their antibiotics irregularly showed beta-hemolytic streptococci on a number of occasions. Both of them were sleeping with siblings who had not had rheumatic fever and were carrying beta-hemolytic streptococci. All 3 of these people had been instructed to take antibiotics daily. The older girl had discontinued it almost a year previously because she felt perfectly well and saw no need of taking medications when she was not sick. The younger 2 were supposed to take antibiotics but were inclined to forget them unless reminded by their mother.

All 3 families were living in crowded conditions. It is reasonable to assume that all members of the family were intimately exposed whenever anyone in the family had streptococci in his throat. Despite this, the subjects showed a very marked variation in the way they handled their exposure to streptococci. Thirteen of the 25 subjects never showed beta-hemolytic streptococci in their pharyngeal cultures. Five had positive cultures rarely

and the organisms were present only transiently, quickly disappearing. Four showed positive cultures intermittently through the first month and a half of study. And 4 of the subjects, once their cultures were positive, continued to have positive cultures fairly constantly until the organisms disappeared from all members of the family. The investigator who collected swabs from all of these throats was constantly exposed to beta-hemolytic streptococci. Periodic swabs of his throat never grew out cultures of beta-hemolytic streptococci.

V. SOME FACTORS AFFECTING RESISTANCE TO BETA-HEMOLYTIC STREPTOCOCCAL INFECTION. There are many factors which are considered to affect individual resistance to infection with streptococci. The ones studied in this project were the general state of nutrition as indicated by height, weight, and hemoglobin level and the immune response of the individual as indicated by the ASO titers. This information is given in Table 4.

ASO titers were obtained during the third week of the study and again at the end of the study. Most of the variations observed were only a single tube dilution in one direction or the other. At the end of the study, the ASO titers did show a difference in the different groups as would have been anticipated. Thus, those subjects who had had constant or frequent positive cultures for beta-hemolytic streptococci had higher titers than those whose cultures were positive rarely and transiently. These, again, were higher than the subjects who did not show positive cultures at any time. A striking exception to this general pattern was exhibited by a 9-year-old girl in Family B who was on

TABLE 4.—NUTRITIONAL STATUS AND ASO TITERS OF SUBJECTS

Pattern of Positive Cultures	*Family*	*Sex*	*Age*	*ASO*	*ASO*	*Hb*	*Ht*	*Wt*	*Percentile* *Ht*	*Percentile* *Wt*	*Remarks*
Constant	L	F	16	100	125	11.0	62½	100	40	30	
	B	F	11	166	333†	11.9	59	87½	90	85	
	B	F	6	250	333†	11.6	47½	51½	80	80	
	B	F	4	125	125	11.7	41½	36	75	50	
Intermittent	L	F	15*	125	250	11.7	58	75½	5	3	Irreg. anti.
	L	M	11*	12	100	11.1	59	78	90	60	Irreg. anti.
	L	F	13	250	166	11.7	62	110	70	70	
	L	M	7	333	250†	11.3	46	50	10	50	
Rare and transient	L	F	40	50	12†	12.0	65	149	—	—	
	L	M	4	125	250	11.1	41½	41	50	90	
	B	F	16	500	500	12.6	63	126	50	60	
	S	M	14	125	166†	14.0	66	123	80	80	
	S	M	12*	50	50	12.6	57	87	25	50	On antibiotics
Never	L	M	47	50	125	13.5	60	150	—	—	
	L	F	19*	333	50	11.9	61	109	30	40	Not on antibiotics
	B	M	42	12	12	15.4	70½	162	—	—	
	B	F	38	125	100	12.1	65	178	—	—	
	B	M	18	166	50	14.1	69½	198	50	99†	
	B	F	13	50	50	11.9	62	121	70	90	
	B	F	9*	333	500	10.9	50	52	45	40	On antibiotics
	S	F	31	250	100	13.1	62	152	—	—	
	S	F	10*	100	12	10.9	53	70½	50	60	On antibiotics
	S	F	8	12	12	11.8	49½	50	50	40	
	S	M	6*	166	125	12.6	45	48	50	75	On antibiotics
	S	F	5	12	12	13.1	40	37	20	50	

* Had had rheumatic fever.
† Streptococci demonstrated between determinations.

antibiotics regularly and showed no positive cultures during the course of the study. Her titer started high and rose one dilution, despite the lack of positive cultures, to become 1:500 at the end of the study.

The hemoglobin determinations were of some interest. It will be noted from Table 4 that the subjects who had constant or intermittently positive cultures for beta-hemolytic streptococci all had hemoglobin levels below 12 gm. The majority of subjects showing rare or no positive cultures for beta-hemolytic streptococci had hemoglobin levels of 12 or above. The 2 striking exceptions were 2 girls with hemoglobin levels of 10.9 gm. who never showed positive cultures for beta-hemolytic streptococci. Both of these girls, however, had had rheumatic fever and both were taking antibiotics daily.

Analysis of the height-weight data did not disclose any correlations with the presence or absence of beta-hemolytic streptococci in the pharyngeal cultures.

VI. pH AND STRESS. The correlation between pH and stressful events or emotions was difficult to make from the data obtained since pH varies rapidly from minute to minute and the events recorded were taken from a diary of day-to-day events. Despite this, there were many bits of evidence suggesting that pharyngeal pH was responsive to stressful situations and their attendant emotional reactions. Table 5 gives data for a few selected days taken from the records of Family B.

The average pH for Family B throughout the period of study was 6.6. A tranquil day when things were running smoothly is given as a baseline for comparison. Though slight individual variations were noted, none of these were marked and the average for the day was 6.6. The lowest figure for this day was in the 18-year-old boy who was having minor troubles with his motor scooter. The other children seemed to be playing happily and there were no major disturbances within the family as a group. On the day marked "father irritable" the whole family was disturbed. He was dissatisfied with his job and was quite irritable as a result. The entire family responded to his irritability and all pH values except for the youngest child were depressed, some of them markedly so. A number of similar records could be drawn from this study to illustrate variations in pH associated with stressful events.

TABLE 5.—pH ON SELECTED DAYS IN FAMILY B

	M 42	*F 38*	*M 18*	*F 16*	*F 13*	*F 11*	*F 9*	*F 6*	*F 4*	*Average*
Average for all days	6.8	6.5	6.5	6.5	6.4	6.5	6.6	6.8	6.7	6.6
Tranquil day	6.9	6.6	6.2	6.6	6.4	6.3	6.7	6.6	6.8	6.6
Father irritable	6.2	6.3	6.4	5.7	5.9	6.0	6.2	5.5	6.8	6.1
Everyone upset	6.9	6.9	6.0	6.5	6.4	6.5	6.7	7.1	6.7	6.6

However, it was also possible to find days in which considerable stress was present and pH readings were normal. The day recorded in Table 5 as "everyone upset" was such a day. On this day the father was angry at his daughters for staying out too late the night before. The mother was irritable and tired from working and upset that ink had been spilled on the furniture. The oldest boy had had a hard day at work and was irritable, as was the oldest daughter. The 13 and 9-year-old daughters got into an argument re-

quiring the mother's intervention and the 9-year-old then proceeded to start a fight with the 6-year-old daughter. The 4-year-old was also irritable and cranky. Most of the pH readings on this day were close to the average readings and the average for the family was again 6.6. There is certainly a great deal of difference between trying to appease someone who is unduly critical and irritable and expressing one's own irritation freely. Such differences may explain the different pH readings on these 2 days.

Despite the variability of pH noted, no correlation could be established between pH values, color of pharynx, or bacterial growth. All data gathered in this study were consistent with the interpretation that, though pH might influence bacterial growth, it was not a major factor in determining which organism predominated.

VII. COLDS AND STREPTOCOCCAL GROWTH. Rhinitis can be viewed either as beneficial or harmful. The studies of rhinitis in relation to stress done by Holmes, Goodell, Wolff and Wolf[4] view the discharge which occurs with rhinitis as potentially useful response in that it seems to be a "washing away" of noxious influences. On the other hand, it is frequently stated that the changes in vascularity and secretion of the nasal mucosa observed during rhinitis make the mucosa more susceptible to secondary invasion by bacteria. In the present studies, there were 8 subjects who carried streptococci on several successive cultures. In 5 of these, the beta-hemolytic streptococci disappeared from the throat during the course of a cold. In a 6th subject the streptococci disappeared the day before the cold was first recorded. In the other 2, there was no correlation between appearance or disappearance of streptococci and the occurrence of a cold. Though the disappearance of beta-hemolytic streptococci may have been coincidental, this phenomenon is an interesting one which deserves attention in future studies.

VIII. STRESS AND STREPTOCOCCAL GROWTH. *Family L.* Though the day-to-day activities of the family revolved around the mother, who was responsible for family finances and took over all minor disciplinary measures, yet the father was considered master of the household and everyone responded when he spoke. The family spent many hours together and seemed close-knit. The frequent minor arguments were quickly forgotten. The oldest of the children, a girl of 19, seemed somewhat detached emotionally from the group though still living at home. She seldom was disturbed by anything that happened. Though it was expected that she would get a job, she did her job-hunting in a very desultory way, usually window-shopping instead. The youngest, a boy of 4, seemed likewise to go his own way without entering too closely into family activities. The remainder of the children, however, were very responsive to their parent's wishes and anxious to please them.

The major problems of Family L. were financial. The family was struggling to maintain and improve itself. Mr. L. had two jobs, one as custodian at a large department store and the other as porter at an apartment house. Mrs. L. did housework and received about $25.00 a week. She did not dislike housework so long as it did not involve too much ironing. She was usually very irritable at home, however, if the day's activities had been devoted largely to ironing clothes. There were frequent quarrels between the mother and father; but these did not seem to be threatening to the family since the basic relationship between them was good.

Though few days passed without

individual frustrations, certain days stood out as important when viewed in terms of the family as a whole. The sequence of events is recorded in Table 6 and correlated with the number of people showing positive cultures for beta-hemolytic streptococci on each visit during the course of the study. Many of the stressful situations for Mr. L. occurred at work. He was often given extra work to perform and felt that the additional load was an imposition related to his race. On October 9 he was put on a new job with which he was unfamiliar. He was very irritable at home as a result. On October 20 he was pleased to learn that his work was to be changed again and he would be doing work he enjoyed with relatively little supervision.

It was of interest that the important stresses to the family involved the parents, who did not show positive cultures, rather than the children, who did. When Mr. L. was very irritable, the children were more apt to show cultures positive for beta-hemolytic streptococci. When the children were irritable with each other or having difficulties which did not involve the parents this was not true.

In this formulation, it is plain that the father is a crucial figure. When he is disturbed and irritable, the whole family is affected. If there is a relationship between the increase in cultures positive for beta-hemolytic streptococci among the children in the family and the irritability of the father, then one would expect to find that the positive cultures occurred in those children most dependent on the parents. Inspection of the data indicated that this was true since the bulk of positive cultures were seen in the more dependent children rather than in the oldest and youngest who were described as less responsive to their parent's wishes.

TABLE 6.—CORRELATION OF EVENTS WITH OCCURRENCE OF BETA-HEMOLYTIC STREPTOCOCCI IN FAMILY L.

Date of Swab	*Cultures with Beta-Streptococci*	*Remarks*
9/25	2	
9/27	2	
		9/28: Father upset by racial discrimination at work; mother furious at him.
10/2	4	
10/4	3	10/4 : Father reprimanded by boss at work.
		10/6 : Mother in auto accident without license.
10/9	4	10/9 : Accident settled. Father on new job.
		10/10: Father irritable due to new job.
10/11	6	
10/15	3	
		10/16: Mother ironing *all* day. Irritable.
10/18	4	10/17: Father panic-stricken by bill collector.
		10/20: Father to get new job. Pleased.
10/23	0	
10/25	0	
10/30	2	10/30: Mother irritable at lack of cooperation from family.
11/1	1	
11/6	0	
11/8	0	
11/14	0	

Family B. As in Family L., finances and day-to-day discipline in Family B were functions of the mother, though

life revolved about the father when he was home. Though superficially pleasant and easy-going he could be very demanding and obstinate and often made stinging comments about everyone else in the family. He demanded that the family accommodate itself to his whims. Thus, he was the source of many frictions.

and seemed to enjoy being the baby of the family.

The family's economic status was somewhat low, the father working as a garbage collector. They belonged to the Holiness Church and the family was faithful in attendance except for the father who did not attend regularly. There were frequent arguments

TABLE 7.—CORRELATION OF EVENTS WITH OCCURRENCE OF BETA-HEMOLYTIC STREPTOCOCCI IN FAMILY B.

Date of Swab	*Number with Beta-Streptococci*	*Remarks*
9/26	2	
9/28	1	
10/1	2	10/1 : Father tired, irritable, dissatisfied with job.
10/3	2	
10/5	2	
10/8	4	10/6 : 140-mile trip for hay with entire family. Constant bickering of parents in front of children.
10/10	3	
10/12	3	10/11–12: Father berating daughters for late hours.
10/15	3	
		10/16: Dog impounded by dogcatcher. Whole family upset.
		10/18: Father and son arguing about car, upset whole family.
10/19	3	
10/22	2	
10/24	2	
		10/25–26: Much argument over cake-baking for church.
10/26	2	
10/29	2	10/29: Father given new duties; easier work, more pay.
10/31	1	
11/2	0	
11/5	0	
11/7, 9, 12	0	

The oldest girl was resentful of her father's demands and said she would marry to get away from it. The next younger sister, though quieter and more passive in attitude, also was resentful of the father. The 3 "middle" sisters, aged 11, 9, and 6, were largely ignored by both parents. All 3 tried to get their parent's attention: the youngest by teasing and playing pranks and the middle one by frequent complaints of not feeling well. Their efforts were not well received. The youngest child in the family was openly the favorite

between the parents about this. The 18-year-old boy was working and buying a car for the family; but he was not allowed to use the car since the father felt that he was not old enough nor responsible enough to do so. The father also was disturbed by his daughters. The 16-year-old daughter was engaged and the father was frequently upset by the late hours which she and her sisters kept on their dates. Table 7 summarizes the stressful events surrounding the father's relationship to his family and the incidence of positive

cultures for beta-hemolytic streptococci.

Mr. B., like Mr. L., was dissatisfied with his job and resentful that he could do no better. He often threatened to quit though he could not afford to do so. His dissatisfaction varied from time to time depending upon how things went at work. In addition to this, there were frequent arguments between the father and other members of the family. Usually the family sided against him in these arguments. This did not seem to deter him, however. As will be seen from the table, there were many difficulties surrounding the job, the arguments between the 2 parents, and the difficulties between father and children during the first month of the study. A considerable change occurred on October 29 when the father was given the job of driving the garbage truck, which was easier work at more pay. Though minor difficulties occurred following this, he was in a better humor than usual until the day of the last swab. This was the last day that he was to work as truck driver, since the regular driver was returning from vacation. The evidence in Table 7 would suggest again that there is some correlation between the incidence of positive cultures and the state of mind of the father of the family.

Table 5 presented pH data collected in Family B, demonstrating a general decrease in pH values on a day when the father was unusually irritable. Table 7 demonstrated the continuing occurrence of cultures positive for beta-hemolytic streptococci during the weeks of repeated frictions and irritations. The positive cultures occurred in the children who had strong emotional ties to the father, whether expressed by trying to gain his attention through physical symptoms or pranks or by being babied. The children in family B who were openly resentful and rebellious, like the independent but not rebellious children in Family L, had few or no positive cultures.

Family S. In Family S the father was practically excluded from the family group. He was partly responsible for this himself by leaving the family to drink beer or go squirrel hunting. But even apart from this, it was noted that the family regularly reacted adversely to him and seemed to get along better when he was not present. He was the only person in the 3 families who refused to participate in the studies. During the 2 months of study there were only 2 cultures positive for beta-hemolytic streptococci in this family, one each for the 14- and 12-year-old boys. The 14-year-old boy worked at a florist shop and kept a flower garden at home. He particularly liked art at school and particularly disliked mathematics. The day on which he showed beta-hemolytic streptococci in his throat was a day when he was unable to go to work at the florist shop because he had to do his math lessons.

Discussion. Hinkle and Plummer, working with an adult population, concluded that those individuals who were prone to have multiple illnesses, including infectious diseases, were those with a high degree of insecurity. Though no clinical infections occurred in the families reported here, cultures positive for beta-hemolytic streptococci were most common in those children who were more dependent on expressions of approval from their parents. In addition, positive cultures in these children tended to occur when their security was threatened: that is, when the father was irritable and demanding as a result of difficulties at work. The more independent children showed fewer positive cultures.

An association of cold weather with an increased incidence of clinical infections is well validated and has often

been ascribed to the crowding which occurs with inclement weather. Such crowding not only increases the intimacy of exposure but also increases the intensity of family frictions while decreasing the possibility of avoiding these frictions by leaving the house. In the present study, the onset of cold weather was associated with a decrease in the frequency of positive cultures despite a reported increase of clinical infections in the community. However, the data indicate that internal family frictions decreased with the onset of cold weather for reasons bearing little relationship with the climate.

The mechanism whereby stress affects bacterial growth in the pharynx is not clear from the present studies. pH is responsive to emotional circumstances, as evidenced by the data in Table 5; and the situation described there in association with decreased pH seems similar to those which were also associated with an increased incidence of positive cultures. Direct correlation between pH and the appearance of beta-hemolytic streptococci in the pharynx was poor, however, with only a slight decrease at such times from average pH's observed under tranquil conditions. It would appear, therefore, that local factors in the pharynx other than pH were significant in determining whether exposure resulted in positive cultures or not. It was evident, for example, that different individuals handled exposure in diverse ways despite similar pH ranges and that the same individual responded differently under different emotional circumstances. Were this not true, 2 individuals sleeping together should either carry these organisms consistently or not have them present at all.

Conclusions. In the 3 families studied it appeared that: 1) despite intimate exposure to beta-hemolytic streptococci not all individuals demonstrated these organisms in their cultures; 2) changes in the bacterial flora of the pharynx could not be explained in terms of exposure, climate, pH, or color of the pharynx; and 3) a correlation appeared to exist between stresses which affected the family as a group and the appearance of positive cultures. In this relationship, the father appeared to be a crucial figure; the pertinent situation appeared to be one in which the father was irritable and demanding as a result of stresses to which he had been subjected; and the most vulnerable individuals seemed to be those who were most insecure in their relationship with him. The data do not permit this formulation to be offered in more than tentative fashion to be corroborated later.

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(Interlingua on page 6)

OSTEOSCLEROSIS IN CHRONIC RENAL DISEASE

By Horace L. Wolf, M.D.

AND

John V. Denko, M.D.

(From the Departments of Medicine and Pathology, Northwest Texas Hospital, Amarillo, Texas)

Bone changes associated with various types of acquired and congenital renal lesions are well known and have been frequently reported. The change most commonly recognized is a renal type of osteitis fibrosa generalisata with bone absorption and fibrosis (Albright and Reifenstein[2]). Metastatic calcification may also occur in chronic renal disease (Mulligan[11]).

Another uncommonly depicted form of bone change in chronic renal disease is osteosclerosis. Crawford and associates[4] described 3 cases and thought it more frequent than the literature would lead one to believe. Three patients with osteosclerosis were also reported by Ginzler and Jaffe[7]. Claireaux[3] and Davis[5] each reviewed one case. Klemperer[10] stated that bone changes, including osteosclerosis, are not often detectable roentgenologically in the living subject with nephropathy. Follis and Jackson's[6] series of 39 adults with chronic renal failure nearly all showed some degree of "osteomalacia" or osteosclerosis. Ginzler and Jaffe[7] believed that in chronic renal insufficiency bone changes occurred regularly. These consisted of more or less pronounced fibroporotic resorption, fluctuating with new bone formation; the latter may predominate over the years in some cases. Goldbloom and associates[8] have recently reviewed the literature on the hereditary aspects of renal disease, and reported an affected family. Our cases have yielded no evidence for any familial osteosclerosis, deafness, or renal disease.

This is a report of 7 patients with chronic renal disease who developed varying degrees of osteosclerosis.

Case Reports. (Refer to Tables 1, 2, and 3 for laboratory data. Serological test for syphilis was negative in all 7 cases.)

Case 1. A 42-year-old white housewife had an 8-year history of headaches, ankle edema, hypertension, albuminuria, and anemia. She was not deaf. Family history revealed no renal disease, deafness, nor osteosclerosis.

Examination revealed blood pressure 160/78 mm. Hg, facial edema, uremic odor to the breath, epistaxis, and scattered ecchymoses over the extremities.

A review of retrograde pyelograms done 4 years earlier showed that the renal parenchyma bilaterally was thinner than normal. Chest roentgenogram on her final admission disclosed as the only abnormality some generalized increase in the density of the bony structures of the thorax; skull Roentgen-ray films showed marked frontal hyperostosis and osteosclerosis (Fig. 1).

Symptomatic management was carried out. She became progressively worse and quietly expired.

Pertinent necropsy findings: The body was well developed, and nourished. There were numerous cutaneous petechiae and ecchymoses. Both kidneys were very small, the right weighing only 30 gm. and the left 53 gm. Each had a tan, coarsely granular cortex with irregular lobules between scarred, retracted areas. The renal vessels were patent. Microscopically, the cortex showed a marked fibrosis with many completely hyalinized glomeruli and small atrophic tubules (Fig. 2). The fibrotic stroma had only a few infiltrations of lymphocytes. There were, in thicker portions of kidney, enlarged, highly cellular glomeruli. The arterioles were not unusual

TABLE 1.—HEMATOLOGICAL STUDIES

Case Number	*Age*	*Sex*	*Diagnosis**	*Red blood count million/ c. mm.*	*Hemoglobin gm.*	*White blood count c. mm.*	*Segmented neutrophils %*	*Nonsegmented neutrophils %*	*Eosinophils % %*	*Basophils % %*	*Monocytes % %*	*Lymphocytes % %*	*Westergren erythrocyte sed. rate mm./hr.*
1	42	F	G	3.18	9.25	8,800	76	0	0	0	2	22	—
2	58	M	P	3.84	10.95	4,600	52	2	0	1	9	36	8
3	55	M	P	5.74	12.60	12,500	82	4	0	0	2	12	—
4	64	M	P	4.85	14.25	5,250	49	4	4	1	6	36	34
5	53	M	G	3.89	12.75	4,300	73	2	4	0	2	19	39
6	62	M	G	4.90	15.05	7,000	41	2	0	2	9	46	30
7	21	F	P	3.61	9.65	5,000	55	0	0	0	2	43	—

* G = Chronic Glomerulonephritis
P = Chronic Pyelonephritis

TABLE 2.—URINALYSES

Case Number	*Specific Gravity*	*Albumin*	*Microscopic*	*Sulkowitch*	*Bence-Jones Protein*	*Miscellaneous (urines negative for sugar in all but Case 4)*
1	1.005 to 1.010	2+ to 4+	12 to numerous WBC's per h. p. f.	No precipitate	Negative	———
2	1.017	4+	Addis count/24 hrs. 1.03 billion RBC's, 4 million WBC's, 2 million epithelial cells, 1 million "renal" cells, 100,000 coarsely granular casts, 100,000 hyaline casts	—	Negative	———
3	1.003 to 1.024	1+	Very many RBC's, and WBC's per h. p. f.	No precipitate	—	Phenolsulfonphthalein excretion 1st hour 10.5%. 2 hour total 29.5%
4	1.014 to 1.018	1+ to 4+	Addis count/24 hrs. 42 million WBC's, 2 million RBC's, 0 casts	—	—	Urine sugars trace to 2+, glucose tolerance 88 mg. per 100 ml. fasting, 150 mg. per 100 ml. at 2 hrs.
5	1.016 to 1.025	trace to 2+	Addis count/24 hrs. 100,000 coarsely granular casts, 2 million WBC's, 1.0 million RBC's.	—	—	———
6	1.013	3+	Occasional hyaline and finely granular casts, 0–2 WBC's/h. p. f.	Moderate amount of precipitate	Negative	———
7	1.001 to 1.007	Persistent, usually 4+	Numerous WBC's/h. p. f.	Slight amount of precipitate	—	———

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although the larger blood vessels had thickened walls. Three parathyroid glands were found. One of them was enlarged to 6 × 6 × 5 mm. Microscopically hyperplasia of chief cells was predominant (Fig. 3). Bone from the iliac crest, vertebrae, ribs, sternum and femur was dense, hard, and whitish. Histologically there was dense proliferation of mature bone in the cortical portions (Fig. 4). Thickened irregular spicules of bone were present in the deeper levels (Fig. 5). No osteoclastic absorption or extensive fibrosis was evident. Nodular foci of marrow hyperplasia were noted in the iliac crest (Fig. 5). Osteosclerosis was evident in every bone examined, varying in degree, with the denser bone being towards the cortex. There was some old periosteal bone formation. Final necropsy diagnoses were chronic sclerosing glomerulonephritis and diffuse osteosclerosis of bone.

CASE 2. A 58-year-old white man complained of suprapubic pain, low grade fever of 6 months' duration, hip and back stiffness,

Fig. 1.—Case 1. Skull film shows osteosclerosis of frontal and petrous bone areas.

TABLE 3.—BLOOD CHEMISTRY DETERMINATIONS

Case Number	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Total serum protein, gm.%	5.4	6.35	—	7.00	—	7.56	5.39
Albumin, gm.%	3.59	3.34	—	4.21	—	4.48	2.98
Globulin, gm.%	1.81	3.01	—	2.79	—	3.08	2.41
Urea clearance, % normal	—	39	—	67.4	—	69.8	—
Serum Chloride, mEq./L.	—	101.9	—	115.3	112.9	105.7	95.7
Plasma CO2, mEq./L.	—	19.3	—	19.5	18.7	19.5	6.1
Serum Sodium, mEq./L.	—	142	—	140.5	139.5	152.7	138
Serum Potassium, mEq./L.	—	4.1	—	4.22	4.0	4.1	4.76
Serum Calcium, mg. per 100 ml.	9.4	9.17	7.9	10.2	9.52	9.96	4.6
Serum Phosphorus, mg. per 100 ml.	4.4	3.41	2.8	3.74	2.69	2.88	12.88
Serum Alkaline Phosphatase, Bodansky units	15.0	3.8	3.8	3.02	1.88	4.2	0.144
Serum Acid Phosphatase, Bodansky units	8.0	0.0	0.8	0.48	0.53	0.38	0.892
Nonprotein Nitrogen, mg. per 100 ml.	180	56.1	—	76.8	51	48.6	251.4
Urea Nitrogen, mg. per 100 ml.	—	—	31	—	—	—	—
Creatinine, mg. per 100 ml.	—	—	—	—	—	—	9.38

and mild finger joint pains. Nine years previously there had been 4 plus albuminuria with cylinduria which had "cleared" following a course of treatment with a sulfonamide and penicillin. Poor hearing, progressive, had been noted for "a long time." Another urinalysis 3 years previously was reported as normal. For 26 years he had been a furnace man at a local zinc smelter; all employees there are checked periodically for exposure to lead and his health record showed no evidence of plumbism. Specific questioning elicited no family background of deafness, kidney trouble, or "dense bones."

Physical examination revealed a well nourished, well developed man who did not appear ill. Blood pressure 160/80 mm. Hg. Positive findings were complete edentia, and slight limitation of trunk flexion.

Cystoscopy and bilateral retrograde pyeloureterograms (Fig. 6) revealed a normal outline of the upper urinary tract and osteo-

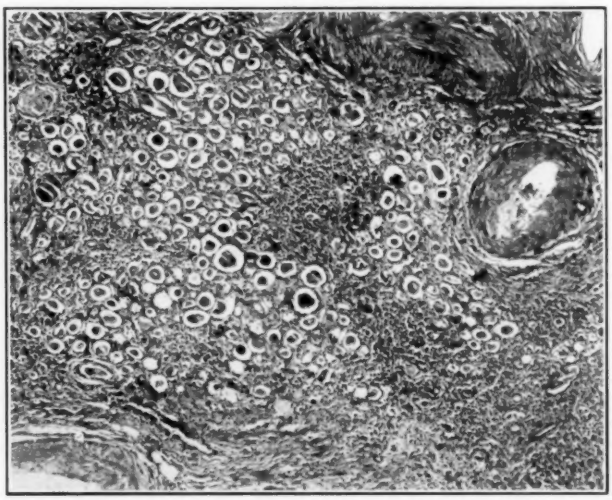

Fig. 2.—Case 1. Kidney showing chronic sclerosing glomerulonephritis. × 63.

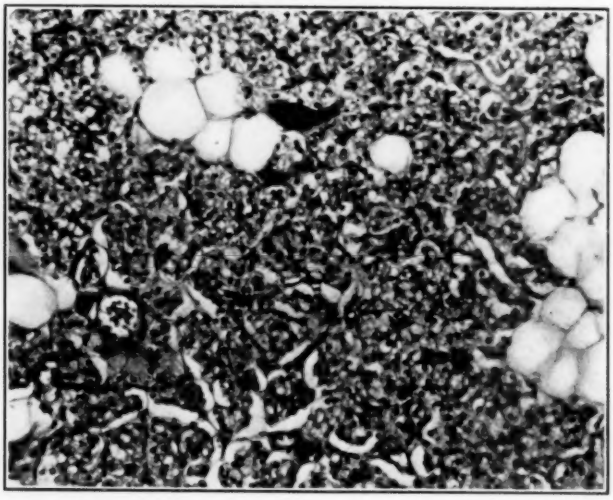

Fig. 3.—Case 1. Parathyroid gland showing hyperplasia. × 155.

sclerosis of the lumbar spine. Bladder and both ureteral orifices were normal. A roentgenogram of the chest showed moderate pulmonary fibrosis with a generalized increase in the density of the bones of the thorax. Roentgenographic studies of the abdomen and pelvis disclosed similar osseous changes of the sacrum.

Peripheral blood and bone marrow smears: Normochromic erythrocytes showed minimal anisocytosis. Platelets were numerous and larger than normal. The neutrophils were mature. Lymphocytes and monocytes presented no changes. The bone marrow films disclosed normal erythroid and myeloid cells in various stages of hematopoiesis. No plasma

Fig. 4*A*—Case 1. Osteosclerosis of iliac crest. Deeper bone spicules are thickened and irregular. × 63 (H. & E.).

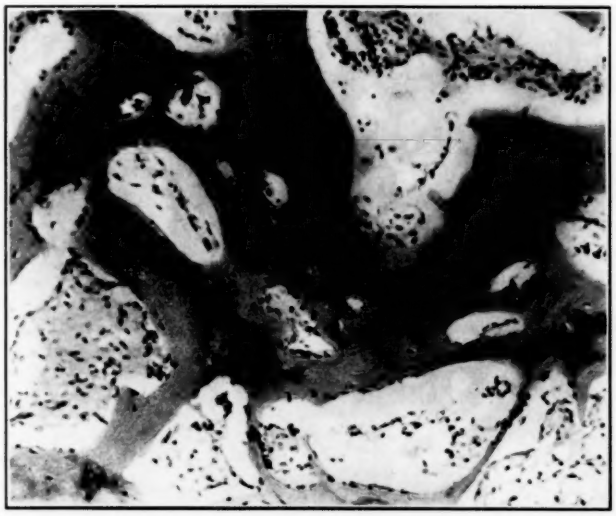

Fig. 4*B*.—Case 1. Vertebral osteosclerosis. Dense proliferation of mature bone near the cortex. × 63. (H. & E.).

cells or metastatic tumor cells were found. Megakaryocytes were numerous.

A bone biopsy from the dense iliac crest had a thickened cortex of lamellar bone with underlying, merging wide adjacent spicules. The bony spicules showed some layering of osteoid along their thickened margins. There was also some formation of thinner spicules of osteoid bone extending into the cellular marrow. The diagnosis was osteosclerosis.

The clinical diagnoses in this case were chronic pyelonephritis and generalized osteosclerosis. In the summer of 1957 his condition was essentially unchanged, and he had been able to continue his work at the smelter.

CASE 3. A 55-year-old white man complained of back pain and generalized muscular aches, weight loss, recurrent bouts of fever, headaches, poor vision, dyspnea, coughing spells, chest pain, leg and pedal swelling,

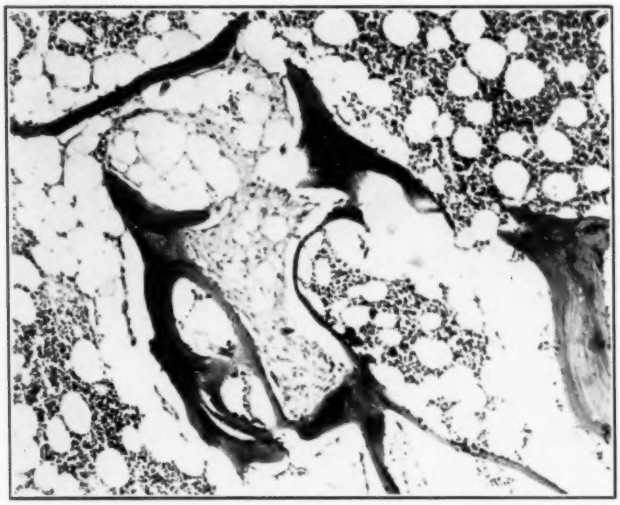

Fig. 5.—Case 1. Iliac crest in deeper levels, showing thickened, irregular bone spicules and nodular foci of marrow hyperplasia. × 87.

Fig. 6.—Case 2. Retrograde pyelogram, with lumbar spine showing osteosclerosis.

nocturia, and a tendency to easy bruising. Five years previously pyuria had been reported. Hematuria had occurred 2 years before this admission. He had good hearing. No familial diseases were known to the patient.

He was a poorly nourished, poorly developed, chronically ill white male. Vital capacity was 2.6 liters, or 66% of normal for his height and age. Blood pressure was 186/116 mm. Hg. Purpuric areas were present over the right forearm. The fundi showed nicking of the veins at the arteriovenous crossings, and blurred optic disc margins. Anteroposterior diameter of the chest was increased. A slight scoliosis of the thoracic spine convex to the left was present.

Roentgen ray studies: The chest roentgenogram revealed generalized increase in density of the thoracic cage. There was osteosclerosis of the sacrum and upper lumbar vertebrae. Retrograde pyelograms were compatible with a diagnosis of severe chronic pyelonephritis. Skull roentgenograms were normal. The right tibia and fibula showed some periosteal proliferation.

A urological consultant reported bilateral chronic pyelonephritis with cystitis and ureteritis cystica. Electrocardiogram suggested left ventricular hypertrophy.

Bone biopsy from the iliac crest showed thickened cortical lamellar bone with dense wide spicules. There was no unusually active osteoblastic proliferation or osteoclastic absorption. The cement lines were not prominent. The marrow portion was cellular with hematopoietic cells. The outstanding feature was the presence of the thickened, dense cortex of mature bone.

Clinical diagnoses were chronic pyelonephritis with cystitis, ureteritis cystica, and osteosclerosis.

The patient was returned to his home on chloramphenicol for further management by his family physician.

CASE 4. A 64-year-old retired white man complained of "gas." Fifteen years previously, while working in a zinc smelter, he began to lose weight; a urinalysis showed "pus, blood and albumin." He was not aware of elevated blood pressure at that time. The albuminuria had persisted ever since, with periodic nocturia and a sensation of incomplete emptying after voiding. He had noticed weakness of his legs and knees with nocturnal leg cramping and painful thumbs. While his appetite was good, he suffered with flatulence. He had infrequent headaches and occasional dizziness, moderate shortness of breath on exertion, occasional palpitations, and swelling of the feet and ankles a year previously. His hearing was "85% of normal." Family history disclosed deafness for one brother and an uncle but no renal disorders or osteosclerosis.

Physical examination showed a large, moderately obese, white elderly male who had a peculiar, greyish yellow complexion. Blood pressure was 168/72 mm. Hg. The retinas showed a grade II arteriosclerosis. The prostate was enlarged, and exquisitely tender; the smear was loaded with pus, due to a subacute prostatitis. Limitation of flexion of the right knee was present.

Roentgenogram studies: A retrograde pyelogram revealed rather small kidneys, but no calculi. Roentgenograms of the abdomen disclosed a normal gas pattern. The soft tissues were fairly well outlined and appeared normal. There were multiple calcifications in the pelvis which had the appearance of phleboliths. There was a generalized increase in the density of the lumbar spine, but the bony trabecular pattern was fairly well maintained. There was moderate osteoarthritis, but no destructive process of the bone. The pelvis also showed osteosclerosis. Upper gastrointestinal tract roentgenographic studies were normal. An electrocardiogram disclosed only frequent ventricular premature systoles.

Biopsy reports: A kidney biopsy was examined at several levels and in the cortex there were scattered hyalinized glomeruli, while large numbers of glomeruli had a normal cellularity and the usual vascular pattern in thin capsules. Those that were hyalinized were all similar, being dense, poorly cellular, and avascular. The stroma had increased amounts of collagen with infiltrations of lymphocytes. The arterioles showed no remarkable alterations. The tubules had cuboidal lining cells. Iliac crest biopsy; the decalcified bone had along its surface some fibrocollagenous tissue. The cortical lamellar portion was thickened. The Haversian canals were prominent. There was no reactive osteoblastic bone proliferation or osteoclastic absorption.

Diagnoses: Chronic pyelonephritis, osteosclerosis, mild diabetes mellitus. His condition was unchanged as of the summer of 1957, six months after the above studies.

CASE 5. A 53-year-old white, zinc-smelter furnace-man complained of left hip and low back pain with sciatic radiation. His hearing was slightly impaired. The genetic history disclosed no deafness nor osteosclerosis; one brother died of "Bright's disease."

Physical examination revealed a well-nourished, well-developed man who did not appear acutely or chronically ill. Blood pressure was 130/90 mm. Hg. Severe pyorrhea

alveolaris and poor dental hygiene were present. There was spasm and stiffness of the lumbar spine area with tenderness over the left sciatic nerve accompanied by diminished straight leg raising. Neurological findings were otherwise negative. Spinal fluid study disclosed a protein level of 127 mg. per 100 ml. and sugar 53.9 mg. per 100 ml. Spinal fluid serology was negative. Colloidal gold curve showed 0011200000, and there were no cells found on microscopic study. A diagnosis was made of a herniated nucleus pulposus.

Roentgen studies: A Roentgen-ray examination of the chest showed a generalized increase in bone density of the ribs and thoracic spine. There were mild degenerative changes of the margins of the mid and lower thoracic vertebrae apparently secondary to old epiphysitis. The lumbosacral spine also revealed an increase in density with narrowing of the lumbosacral space and osteoarthritic spur formation of L–2, L–4, and L–5. An increase in the bony density of the pelvis was noted. The left femur showed a little roughening and irregularity of the periosteum over its posterior aspect. There were 2 or 3 small bony defects of the roof of the acetabulum. Intravenous pyelograms were normal except for bone changes as noted above.

Biopsy of the iliac crest confirmed the osteosclerosis.

Clinical diagnoses were chronic glomerulonephritis, osteosclerosis, and herniated nucleus pulposus. Nine months after study he is continuing at light work.

CASE 6. A 62-year-old white man was referred because of persistent albuminuria and left costovertebral angle pain. Episodes of mild hypertension had occurred over 6 years. Low back, nuchal, and left knee pains, aggravated by damp weather, had been noted for 2 to 3 years. Six years before admission several renal calculi had been passed.

Examination revealed normal blood pressures during hospitalization and no retinal lesions. The only significant findings were left costovertebral angle tenderness on active back motions, and knee crepitations.

Roentgenograms revealed osteosclerosis of the lumbosacral spine and pelvis with marked osteoarthritic spurring of the lumbar vertebrae. Retrograde pyelograms and urological consultation showed a normal right kidney, and a small left kidney, probably due to chronic glomerulonephritis.

Iliac bone biopsy confirmed the diagnosis of osteosclerosis. He has been able to continue at full time duties.

CASE 7. A 21-year-old white woman had plastic surgery for a spina bifida at birth. Clubbed feet, and urinary and fecal incontinence had been present since birth. Repeated urinary tract infections had occurred since infancy. Hearing had always been excellent. Family history elicited no renal disorders nor bone diseases; the maternal grandfather had been deaf.

Examination revealed typical uremia, with facial edema, coma, and convulsions. Blood pressures were repeatedly low normal. Cystometric studies by a urological consultant had earlier confirmed a neurogenic bladder; retrograde pyelograms were considered too dangerous to perform.

Roentgenographic examination demonstrated a spina bifida of L–4, L–5, and S–1 with generalized sclerosis of the lumbar vertebrae, ribs, and pelvis.

In spite of symptomatic therapy, sedation, and attempts at maintenance of fluid balance, she expired. Permission for necropsy was refused. Final clinical diagnoses were chronic pyelonephritis, secondary to neurogenic bladder (spina bifida), and osteosclerosis.

Discussion. The 7 patients presented all had clinical and laboratory evidence of chronic renal disease ranging from 5 to 20 years' duration; chronic glomerulonephritis was diagnosed in Cases 1, 5, and 6; chronic pyelonephritis in Cases 2, 3, 4 and 7.

Recent literature has stressed genetic relationships in chronic Bright's disease (Goldbloom *et al.*[8]). Our case series disclosed minimal deafness in Cases 2, 4 and 5 (all men), auditory damage in 2 members of the family of Case 4, and "Bright's disease," fatal for a brother of Case 5. No family history of osteosclerosis was elicited in any member of the patients' families. Hence, we find no evidence in our 7 patients for any genetic relationships of chronic renal disease and osteosclerosis. However, minimal hearing loss may be related to the osteosclerosis. Further study is indicated to prove or disprove this possibility.

Roentgenograms showed varying degrees of osteosclerosis in the entire case series. The films reproduced in Figs. 1 and 6 demonstrate these

changes best in photographs for publication.

The lumbar vertebrae were involved in all 7 cases; the thoracic cage in Cases 1, 2, 3, 5 and 7; the sacrum in cases 2, 3, and 6; the pelvis in all but Case 3 and skull and femurs only in Case 1.

Laboratory review disclosed anemia in Cases 1, 2, and 7. Nonprotein (or blood urea) nitrogens were elevated in the entire series. Serum calciums were low in Cases 3 and 7, because of marked renal acidosis in the latter patient. Serum alkaline phosphatase was elevated in Case 1 and low in Case 7. The elevated serum acid phosphatase in Case 1 is difficult to explain (technical error?) but is the only such determination available to us (from studies elsewhere).

Metabolic acidosis was present in Cases 2, 4, 5, 6 and 7. Necropsy of Case 1 showed secondary hyperparathyroidism (hyperplasia); this probably also existed in Case 7.

The 7 cases were all seen within a period of 18 months, showing that a combination of chronic renal disease and osteosclerosis is relatively common when one is aware of and looks for this entity. Cases 4, 5 and 6 were brought to our attention respectively by an internist, an orthopedic surgeon, and a urologist who were aware of our interest in this problem aroused by Cases 1, 2 and 3.

In his interpretation of the roentgenograms in Case 7, our hospital radiologist, without knowledge of the full clinical background, and from experience with films in Cases 1 through 6, listed chronic renal disease among the differential diagnostic possibilities as causes for the dense bones seen on her films.

Pathogenesis. Osteosclerosis in chronic renal disease differs from the type of diffuse bone sclerosis found in myeloid metaplasia of the spleen and panmyelosis. The histological pattern in our series does not show the hematopoietic alteration in marrow cells and stroma found in myelosclerosis of nonrenal origin.

In hyperparathyroidism, a generalized bone disease (osteitis fibrosa generalisata) may be present. Likewise, secondary hyperparathyroidism, in the presence of chronic renal disease, may cause "renal osteitis fibrosa generalisata." Rutishauser[12] discussed the role of the parathyroids in the genesis of the mild changes in the bone noted in osteosclerosis accompanying chronic renal disease. But neither he, nor Ginzler and Jaffe[7], believed that the parathyroids played any important role in the genesis of these changes. Rutishauser[12], Ginzler and Jaffe[7], and Albright[1] all accepted the following theory: Since the damaged kidney cannot form base, fixed base, including calcium and magnesium, is utilized to eliminate the acid end products of metabolism. The skeleton thus becomes demineralized. During periods of fluctuation of the renal insufficiency and acidosis, new bone deposition occurs, occasionally resulting in osteosclerosis. This theory is the most acceptable one, but the basis of osteosclerosis developing in patients with chronic renal disease is not clear in many respects. Dietary factors, fluorine content of drinking water (Johnston[9]), hormonal changes, and alterations in renal function and blood chemistry must be studied in more detail and at periodic intervals in these patients to be able to understand and explain the bone changes that develop.

Summary. 1. Osteosclerosis may accompany chronic renal disease. A partial review of the literature has shown that this entity has not been reported frequently. 2. We have pre-

sented 7 patients with chronic renal disease who developed varying degrees of osteosclerosis; with complete necropsy findings on one patient, bone biopsy on 5 others, and a renal biopsy on one. The histological pattern of bone was similar in all 6 cases with tissue studies; the sclerosis began in the cortex and extended into the marrow portions. 3. The pathological physiology and the relationship of calcium-phosphorus-parathyroid metabolism to chronic renal disease is not too well understood. We would favor the theory that osteosclerosis may occur in patients with chronic renal disease who first developed varying degrees of bone absorption and then osteosclerosis. These changes are probably related to renal metabolic acidosis.

ACKNOWLEDGMENTS: We are indebted to W. E. Scott, M.D., Amarillo, Texas, for permission to use Case 4, and to Nicholas Leone, M.D., Chief of Medical Investigation, National Institute of Dental Research, National Institutes of Health, Bethesda, Md., for the photomicrographs.

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SUMMARIO IN INTERLINGUA

Osteosclerosis In Chronic Morbo Renal

1. Osteosclerosis pote accompaniar chronic morbo renal. Un revista partial del litteratura indica que iste entitate non es reportate frequentemente.

2. Nos presenta 7 patientes con chronic morbo renal qui disveloppava varie grados de osteosclerosis. Es includite complete datos necroptic pro un del patientes, biopsias ossee pro 5 alteres, e un biopsia renal pro le septime. Le configuration histologic del osso esseva simile in omne le 6 casos assi studiate. Le sclerose comenciava in le cortice e se extendeva a in le portiones medullari.

3. Le physiologia pathologic e le relation del metabolismo parathyroide de calcium e phosphoro con chronic morbo renal es non ancora multo ben comprendite. Nos exprime nos in favor del theoria que osteosclerosis pote occurrer in patientes con chronic morbo renal qui primo ha disveloppate varie grados de absorption ossee. Iste alterationes es probabilemente relationate con acidosis metabolic renal.

THE TRANSPORT OF URIC ACID IN SERUM*

By J. E. Morris, M.D., M.R.C.P.

(From the Department of Biochemistry, University of Manitoba Medical School and the Winnipeg Clinic, Winnipeg, Manitoba)

The concentration of uric acid as measured by the Folin[5] method is known to be greater in serum and plasma than in their ultrafiltrates. Several workers (Adlersberg, Grishman and Sabotka[1], Lambie[8], and Wolfson, Levine and Tinsley[12]), have also observed that the ultrafilterable portion of serum uric acid varies in each individual sample. Wolfson[12] examined the serum of two normal individuals and found 70 to 85% of the uric acid was ultrafilterable when the determination was made by the Folin method alone or after incubation with uricase.

This variability has prompted this study of the uric acid content in a series of serum samples taken from individuals in health and disease. Each specimen was ultrafiltered and analysed for uric acid chromogen both before and after the action of uricase. In order to ascertain what determined the degree of ultrafilterability of uric acid in serum, the samples were examined by filter paper electrophoresis to determine the location and the characteristics of the uric acid chromogen.

Material and Methods. Serum samples were obtained from 15 normal subjects and 13 patients with either hyperuricemia or abnormalities in their serum proteins. The pathological conditions which provided the abnormal sera were chronic nephritis, uremia, leukemia, liver disease and gout.

Serum ultrafiltrate was obtained by pressure filtration of serum through cellophane (Cenco #70160), using a plastic-lined apparatus of similar design to that used by Nicholas[9]. Ultrafiltration was carried out at room temperature using nitrogen at a pressure of 60 pounds per square inch and the ultrafiltrate was collected in a sterile tube. All ultrafiltrates which were contaminated with protein were discarded.

The uric acid concentration was measured by Brown's modification[3] of Folin's method.

One milliliter samples of serum and ultrafiltrate were analysed for uric acid chromogen and then incubated with 10 mg. of uricase powder at pH 9.0 at 45° C. for 90 minutes after which the residual uric acid chromogen was determined. The uricase was prepared from fresh beef kidney (Buchanan, Block and Christman[4]) and its potency maintained by storage *in vacuo*. Assays showed that 5 mg. of dried uricase powder gave no chromogen after incubating at pH 9.0 for 90 minutes with 2.77 micromoles of uric acid.

The albumin and globulin concentrations in serum were estimated by the biuret method of Kingsley[7].

ELECTROPHORESIS OF SERUM AND ULTRAFILTRATE. The electrophoresis of serum and ultrafiltrate was performed in Palitzch's borate buffer at pH 8.6 (550 ml. M/20 borax with 450 ml. M/5 boric acid). Applications of 0.02 ml. were made to strips of filter paper (Schleicher and Schüll 595) one cm. wide and a potential difference of 100 to 150 volts applied. A current flow of 0.6 milliamperes per strip was maintained. The apparatus permitted the electrophoresis of 12 strips simultaneously under identical conditions. A satisfactory separation of serum proteins detectable by bromphenol blue staining occurred in 4 to 6 hours.

Uric acid chromogen was demonstrated on the dried filter paper strip by the following technique. The strip was gently moistened by a pledget soaked with a solution containing equal parts of 50% urea and 12% sodium cyanide. While still damp, Folin's uric acid reagent was vaporized onto it from an all glass spray. Within a minute a blue band appeared at the site of the uric acid chromogen provided a minimum of 0.5 microgram of uric

*Presented in part at the meeting of the Canadian Rheumatism Association, Quebec City, June, 1956.

TABLE 1.—THE CONCENTRATION OF SERUM URIC ACID, ALBUMIN AND GLOBULIN AND THE PERCENTAGE OF NONULTRAFILTERABLE URIC ACID IN HEALTH AND DISEASE

Patient	*Serum Uric Acid mg./100 ml.*	*Ultrafiltrate Uric Acid mg./100 ml.*	*Percentage Nonultra-filterable Uric Acid*	*Serum Albumin gm./100 ml.*	*Serum Globulin gm./100 ml.*	*Condition*
1	5.45	4.4	19.3	4.7	2.6	Normal
2	2.75	2.5	0.9	4.5	1.8	Normal
3	5.0	2.45	51.0	5.7	1.5	Normal
4	3.2	2.2	31.3	4.8	1.8	Normal
5	4.05	2.35	42.0	5.1	2.0	Normal
6	3.0	1.9	37.0	5.0	1.3	Normal
7	4.35	3.95	9.2	4.7	2.5	Normal
8	4.25	4.15	2.4	4.6	1.7	Normal
9	4.65	3.6	22.6	5.1	2.1	Normal
10	4.6	3.8	17.4	5.2	1.4	Normal
11	3.5	2.5	28.6	4.9	1.4	Normal
12	4.95	4.8	3.0	4.3	2.3	Normal
13	4.2	3.7	11.9	3.4	2.5	Normal
14	3.3	2.6	21.2	4.9	1.8	Normal
15	5.0	3.5	30.0	5.2	2.3	Normal
16	11.9	10.6	11.0	3.9	1.4	Uremia & Nephritis
17	2.55	2.25	11.8	3.8	1.6	Uremia & Nephritis
18	9.6	9.2	4.3	3.7	1.9	Uremia & Nephritis
19	19.4	18.5	4.6	3.8	2.0	Uremia & Nephritis
20	9.25	8.0	13.5	4.2	1.7	Uremia & Nephritis
21	8.75	7.0	20.0	4.4	3.0	Uremia & Nephritis
22	6.7	5.3	20.9	4.3	2.4	Uremia & Nephritis
23	10.2	10.2	0.0	2.8	2.2	Uremia & Nephritis
24	4.7	3.2	31.9	5.0	3.3	Leukemia
25	3.0	1.4	53.3	4.1	3.0	Leukemia
26	4.1	2.7	29.3	3.4	5.6	Cancer of Liver
27	3.5	3.05	12.9	4.0	4.0	Not Diagnosed
28	6.8	6.3	7.3	5.3	2.5	Gout

Fig.

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acid was localized by electrophoresis. When the urate concentration was low in ultrafiltrate it was necessary first to concentrate the liquid by evaporation in air.

Results. The analysis of serum samples from normal individuals and from patients with various disorders is shown in Table 1. The percentage of uric acid chromogen which was not ultrafiltered and remained with the serum protein varied considerably in both groups of sera. Figure 1 shows that a linear relationship exists in each group between the serum albumin con-

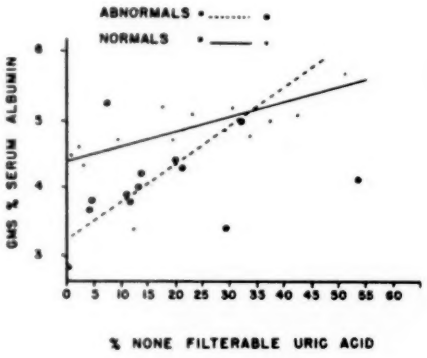

Fig. 1

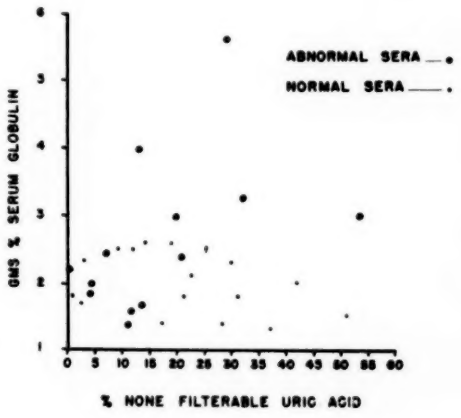

Fig. 2

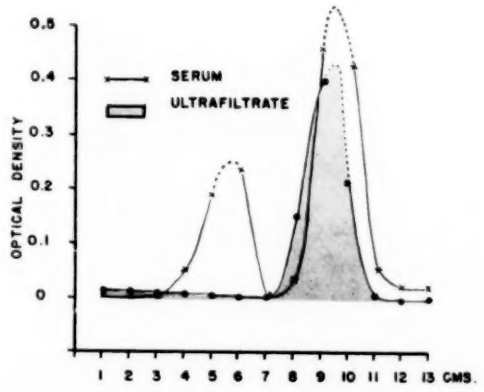

Fig. 3

Fig. 1.—Graph showing relationship of percentage nonfilterable uric acid to serum albumin concentration in health and disease.

Fig. 2.—Graph showing relationship of percentage of nonfilterable uric acid to serum globulin concentrate in health and disease.

Fig. 3.—Graph illustrating positions of chromogenic bands in serum and ultrafiltrate resulting from the electrophoretic separation from the point of origin towards the anode.

TABLE 2.—THE RESULTS OF URICASE ACTIVITY ON SERUM AND ULTRAFILTRATE IN HEALTH AND DISEASE

Patient	Serum Uric Acid (mg./100 ml.)		Ultrafiltrate Uric Acid (mg./100 ml.)		Residual Percentage of		Condition
					Serum Uric Acid Chromogen	Ultrafiltrate Uric Acid Chromogen	
	Before Uricase	After Uricase	Before Uricase	After Uricase			
1	5.45	0	4.4	0.8	0	18.2	Normal
2	2.75	0	2.5	0.55	0	22.0	Normal
3	5.0	0.05	2.45	0.45	1.0	18.4	Normal
4	3.2	0	2.2	0.5	0	22.7	Normal
5	4.05	0	2.35	0.6	0	25.5	Normal
6	3.0	0	1.9	0.1	0	5.3	Normal
7	4.35	0.3	3.95	1.0	6.9	25.3	Normal
8	4.25	0.15	4.15	0.75	3.5	18.1	Normal
9	4.05	0.1	3.6	0.95	2.1	26.4	Normal
10	4.6	0.1	3.8	1.0	2.2	26.3	Normal
11	3.5	0	2.5	0.7	0	28.0	Normal
12	4.95	0.1	4.8	1.1	2.0	22.9	Normal
13	4.2	0	3.7	0.4	0	10.8	Normal
14	3.3	0.05	2.6	0.4	1.5	15.0	Normal
15	5.0	0.15	3.5	0.7	3.0	20.0	Normal
16	11.9	2.45	10.6	3.8	20.6	36.8	Uremia & Nephritis
17	2.55	0	2.25	0.75	0	33.3	Uremia & Nephritis
18	9.6	0.8	9.2	2.3	8.3	25.0	Uremia & Nephritis
19	19.4	2.8	18.5	5.55	14.3	30.0	Uremia & Nephritis
20	9.25	0.1	8.0	1.9	1.1	23.8	Uremia & Nephritis
21	8.75	0.7	7.0	2.6	8.0	37.1	Uremia & Nephritis
22	6.7	0.8	5.3	1.7	12.0	32.1	Uremia & Nephritis
23	10.2	0.95	10.2	3.4	9.3	33.3	Uremia & Nephritis
24	4.7	0	3.2	0.75	0	23.4	Leukemia
25	3.0	0.1	1.4	0.5	3.3	35.7	Leukemia
26	4.1	0.3	2.7	0.7	7.3	25.9	Cancer of Liver
27	3.5	0.5	3.05	0.7	14.3	22.9	Not Diagnosed
28	6.8	0	6.3	2.2	0	31.0	Gout

centration and the percentage of serum uric acid which cannot be pressure filtered through cellophane. It is seen in Fig. 2 that no correlation exists between the concentration of serum globulin and the residual nonultrafilterable uric acid.

The results of uricase activity differed considerably when serum and serum ultrafiltrate were used as substrates. Table 2 indicates that 0 to 6.6% chromogen (mean 1.5%) remained after normal serum was incubated whereas pathological serum provided an increase in residual chromogen up to 20.6% (mean 7.5%). The corresponding ultrafiltrates gave more striking differences both in each group and in comparison with the parent serum. Normal serum ultrafiltrates incubated with uricase gave 5.3 to 28% residual chromogen (mean 19%) and in the abnormal group 22.9 to 37.1% (mean 30%).

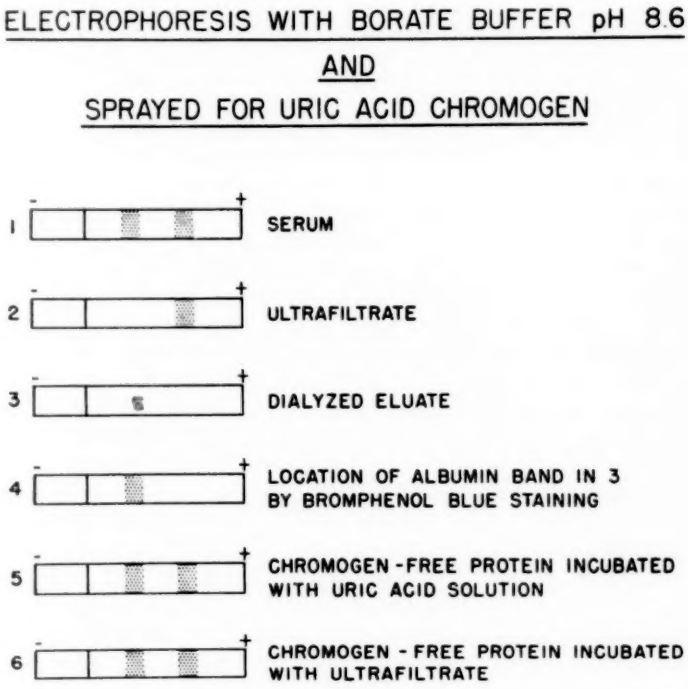

Fig. 4

Fig. 4.—Schematic to show the occurrence of chromogenic bands in various experiments with serum, ultrafiltrate, dialyzed albumin and dialyzed albumin incubated with uric acid and ultrafiltrate.

The electrophoretic analysis of serum and serum ultrafiltrate for uric acid chromogen is shown in Fig. 3. The two superimposed graphs were obtained by eluting serial 1.0 cm. lengths of undeveloped strips and measuring the optical density of the eluate after the addition of Folin's

reagent. The two peaks obtained with serum represent the location and intensity of two chromogenic bands which have migrated from the point of origin towards the anode at different speeds. The more slowly migrating band gives rise to a smaller peak than the faster migrating chromogen which is closer to the anode. With ultrafiltrate a single chromogen band is found in identical position and of similar intensity to the fast migrating chromogen which is present in the serum. If pure uric acid is applied to a control strip and subjected to electrophoresis it produces a band coinciding with that obtained with serum ultrafiltrate. When the protein residue remaining on the cellophane after serum ultrafiltration was electrophoresed and the paper stained for uric acid chromogen and serum protein, a single chromogen was found to coincide with the slower migrating fraction in the serum and to be located with serum albumin (Fig. 4).

The chromogen bands were subjected to ultraviolet absorption spectroscopic analysis. Only the faster migrating band gave a characteristic absorption spectrum of uric acid with a maximum at 293 mμ. The spectroscopic analysis of the other band failed to give a similar absorption curve presumably due to the presence of protein. Because of this difficulty it was necessary to obtain in quantity, material from the band in question. A large number of strips were eluted in this area and the combined eluate dialyzed against running tap water for 48 to 72 hours through cellophane and then concentrated and electrophoresed. In this way pure serum albumin was produced free from uric acid chromogen. The latter was incubated with either a 5 mg. per 100 ml. standard uric acid solution or serum ultrafiltrate for 12 hours at 37° C. and produced two chromogenic bands on electrophoresis identical with that seen with the original serum (Fig. 4).

Discussion. The results of these experiments indicate that uric acid exists in serum in both a protein-free moiety and in one which is albumin bound. This has been suggested by Bennhold[2] who carried out other electrophoretic studies. The affinity of albumin for uric acid in normal individuals appears to be different in diseases in which the concentration of uric acid and protein are disturbed. This binding would seem to be physical rather than chemical because dialysis separates uric acid from albumin. Furthermore, the incubation of pure albumin with uric acid or ultrafiltrate restores the albumin bound complex. By varying the conditions of pH and uric acid concentration Von Pryzlecki and Grynberg[10] found that uric acid was capable of combining with proteins such as casein, gelatin, albumin and globulin. This reaction was a reversible one depending largely on changes in electrolyte concentration. It is pertinent to note that globulin was not found to be associated with uric acid in the experiments reported in this communication. It is possible, however, that the linear relationships depicted in Fig. 1 differ because of changes in electrolyte concentration in the abnormal sera producing differences in the albumin-binding potential for uric acid.

After serum ultrafiltrate is incubated with uricase, the chromogenic residue is always greater than when the parent serum is used as substrate. It is likely that uricase activity is enhanced by the presence of protein or some nonultrafilterable material. Wolfson, Huddlestun and Levine[11] have clearly pointed out that the blue color produced by Folin's reagent is not specific for uric acid but can result from the

reaction of certain reducing agents and also occurs with some substituted purines. However, their observations led to the conclusion that the small concentrations of any of these substances in serum cannot significantly contribute to its chromogenic content. The origin of a nonurate chromogen has been postulated to be endogenous and chemically purine in nature but of unknown composition (Wolfson, Huddlestun and Levine[11]). This concept of endogenous nonuric acid chromogen needs reappraisal in view of these results which demonstrate that the process of ultrafiltration gives rise to a substrate which has more potential chromogen than the parent serum. This is particularly apparent in the estimations performed with uricase. It is difficult to explain how ultrafiltration could have produced chromogen unless the uricase activity was inhibited, perhaps by the removal of a nonultrafilterable activator.

Maxwell Johnstone[6] has found that insignificant quantities of uric acid chromogen remain after normal serum is incubated with uricase but that chromogen increases when the enzyme reacts with abnormal sera. This difference has also been observed to occur in the present study with the respective ultrafiltrates.

The origin of residual chromogen remains obscure but it is possible that the chromogenic material results from a persistence of a degradation product of uric acid. The presence in normal serum of a nonultrafilterable activator for uricase is suggested. This would enable the uricolytic reaction to proceed to completion in serum with the production of a nonchromogenic end product. In abnormal sera the action of the postulated activator may become impaired.

Conclusions. 1. Uric acid is present in serum in two forms, free and bound to albumin.

2. The affinity of uric acid for serum albumin differs in normal and pathological sera.

3. When incubated with uricase serum ultrafiltrate produces more residual chromogen than the parent serum.

ACKNOWLEDGMENTS: This work was supported by grants from the National Research Council of Canada and from the Manitoba Institute for the Advancement of Medical Education and Research (Winnipeg Clinic Research Institute).

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(Intrlingua on page 106)

EXPERIMENTAL HORMONAL THERAPY OF ATHEROSCLEROSIS: PRELIMINARY OBSERVATIONS ON THE EFFECTS OF TWO NEW COMPOUNDS*

By Frank W. Davis, Jr., M.D.
INSTRUCTOR IN MEDICINE

William R. Scarborough, M.D.
ASSISTANT PROFESSOR OF MEDICINE
(RESEARCH ASSOCIATE, HOWARD HUGHES MEDICAL FOUNDATION)

Robert E. Mason, M.D.
INSTRUCTOR IN MEDICINE

Martin L. Singewald, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

AND

Benjamin M. Baker, Jr., M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From the Department of Medicine, The Johns Hopkins University School of Medicine and Hospital, Baltimore, Maryland)

Of the several experimental approaches to the treatment of atherosclerosis, especially coronary atherosclerosis, the administration of estrogenic substances is among the more promising. The fundamental observations of Pick, Katz, and coworkers[5,6] have clearly demonstrated the ability of large doses of estrogen to prevent experimental atherosclerosis in the chick. These workers have also shown that the experimentally induced atherosclerotic lesion regresses under the influence of estrogens. In their studies both protection and regression are limited to the coronary arteries, and the aortic lesions are uninfluenced. The accompanying abnormalities in serum lipid pattern are, in part, reversed.

Extensive observations on the effects of estrogen in humans have been made by Barr, Russ, and Eder[2,8]. Estrogens, both alone and in combination with androgen, were administered to normal and atherosclerotic human subjects, and detailed measurements of their effects on plasma lipoproteins made. Abnormalities of lipoprotein distribution, often present in older normal subjects and in patients with coronary artery disease, could be favorably altered by estrogen administration. Accentuation of abnormality followed the exhibition of testosterone. In some patients with xanthomatosis, the skin lesions decreased in size during estrogen therapy.

These observations, as well as those of other workers similarly engaged in the investigation of hormonal influences on atherosclerosis, correlate well with clinical teachings which have long acknowledged the relative immunity of the normal young female to atherosclerosis

*This investigation was supported in part by a Research Grant (H-327) from the National Heart Institute of the National Institutes of Health, United States Public Health Service.

rotic heart disease. The "protective" effect of estrogen is also suggested by the fact that atherosclerotic lesions increase in frequency in the postmenopausal woman (Ackerman, Dry and Edwards[1]) and in oophorectomized women (Wuest, Dry and Edwards[13]). Despite these encouraging indirect evidences, no proof is yet available which allows the conclusion that estrogen can reverse the established atheroma in human subjects.

The clinical usefulness of estrogen in the human suffering from coronary atherosclerosis is greatly limited by the undesirable side effects of these agents, especially in the large doses which are apparently necessary to assure normalization of serum lipid pattern. This is particularly true in the male, in whom libido and potentia are lost, and gynecomastia appears, but also in the female because of uterine bleeding. Gastrointestinal irritation is common with many of the ordinary estrogens. Attempts to modify the feminizing side-effects by simultaneous androgen administration usually results in loss of serum lipid effects (Russ, Eder and Barr[8]), and thus this approach does not seem promising. Extensive efforts to develop substances capable of producing favorable changes in plasma lipoprotein distribution without inordinate feminization are in process. It is the purpose of this report to summarize some preliminary observations on the effects of two drugs which were designed for this purpose, and to compare their actions with those of conventional estrogens.

Methods and Materials. Sixty-one subjects, 47 men and 14 women, are included in this report. Many of these have been exposed to several of the drugs under study, during separate treatment periods. All are from a larger group of patients under long-range study in this laboratory. All have clinical atherosclerosis, having sustained a myocardial infarction or suffered from angina pectoris, or in several instances, demonstrated severe peripheral vascular disease. Some patients were simultaneously receiving a low-fat diet, but insofar as possible efforts were made to prevent changes of diet during the exhibition of drugs. The test periods varied from several months to several years in duration.

The present evaluation is limited to changes from control status which occurred during a drug test period. Appraisal of clinical effects was on the basis of subjective response, and usually correlated with estimated nitroglycerine consumption. Estrogenic effect was estimated by the patients' statements regarding libido and potentia and by physical examination of the breasts and testicles. Abnormal uterine bleeding was accepted as estrogenic effect (on one occasion dilatation and curettement was necessary, and endometrial hyperplasia was found). Ballistocardiograms and electrocardiograms were recorded and evaluated in a manner previously reported (Scarborough *et al.*[10,11]). The ballistocardiographic response to smoking as a means of stress was based on previously reported criteria (Davis *et al.*[3]). A change in electrocardiographic or ballistocardiographic pattern, or in response to smoking, is reported if it occurred during the test period.

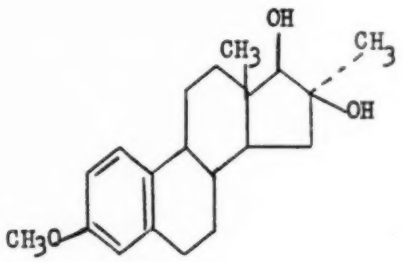
Serum cholesterol levels were determined by the Buell modification of the Bloor method (Thomas and Eisenberg[12]), and the reported changes in total cholesterol represent the mean alteration determined from many observations prior to and during a test period. A mean change of 30 mg. per 100 ml. is arbitrarily reported, although it is realized that this figure may not be significant, especially since the blood was not always drawn in the fasting state.

Lipoproteins were estimated by paper electrophoresis, stained with Oil-Red-O. Results are reported only as gross evaluation of the paper permitted, and alterations reported only where clearly detectable differences were apparent.* Each paper pattern was controlled by the simultaneous determination of lipoproteins in normal serum. Serum proteins were measured in the same fashion, and stained with Bromphenol-blue.

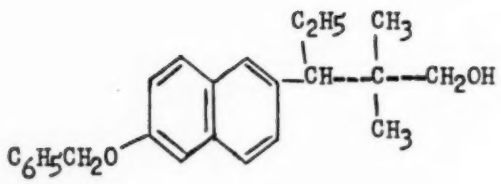
Two experimental compounds were studied, each because of laboratory evidence which suggested the possibility that estrogenic side effects might be less prominent and yet the serum lipid effect of estrogen retained. SC 4289† is a nonsteroidal synthetic com-

*These observations were made by E. W. Smith, M.D.

pound, which initially was felt to have weak influence on serum lipids, and no significant estrogenic action as determined by animal assay. Subsequent animal studies have not confirmed the serum lipid activity. SC 6924 (Manvene)† is a synthetic, oil soluble crystalline powder, which in animals, produces shifts in blood lipids which are generally considered anti-atherogenic. Animal studies indicated estrogenic activity less than 1% that of estrone, with lipid shifting potency which was approximately 20% of that of estrone. The structural formulae of these two compounds is shown in Fig. 1.



SC-6924



SC-4289

Fig. 1.—Structural formulae of the two new compounds reported. SC 6924 (Manvene) is steroidal, and related to other estrogenic substances.

For comparison, 17 subjects (11 men, 6 women) receiving large doses of conventional estrogens (natural and synthetic) are briefly reported. Only patients tolerating doses equivalent to 10 mg. or more of diethyl stilbestrol daily are included.

Results. A. SC 4289. Twenty-three patients were given this compound for an average period of 9.8 months. Each patient is tabulated in Table 1, and a summary of significant changes is presented in Table 2. Clinical improvement occurred in 65%. It is difficult to evaluate this effect, since in some of these patients similar subjective improvement persisted into a subsequent placebo period, or, in a few, appeared during an initial placebo test period. It is doubtful that these results exceed the clinical effects of placebo, although most of the 65% were aware of a definite sense of well-being, and relief of

†SC 4289 and SC 6924 (Manvene) were supplied through the courtesy of Dr. I. C. Winter, G. D. Searle and Company.

TABLE 1.—TABULAR SUMMARY OF THE EFFECTS OF SC 4289

Name	Age	Sex	Diagnosis	Mos. R	Daily Dose mg.	Clinical Result	Estrogen Effect	ECG		BCG		Cigarette Test		Cholesterol		Lipoproteins		Serum Proteins	
								Control	Change	Control	Change	Control	Change	Control	Change	Control	Change	Control	Change
N.A.	56	M	AP	13	40	I	0	abn	I	abn	I	Pos	0	222	+36	B high	B N	A_2 slow	0
P.A.	47	M	AP + MI	10	20	I	0	abn	0	abn	W	B	0	265	+25	B high	B N	A_2 slow	A_2 N
M.B.	46	M	AP + MI	23	40	I	0	abn	I	abn	0	Pos	0	258	+30	+ −	−	−	−
J.C.	38	M	AP + MI	12	20	I	0	N	0	N	I	B	I	325	−75	B N	B high	G & A_2 high	−
G.D.	61	M	AP	8	40	I	0	abn	0	abn	I	Pos	0	273	−40	−	−	−	−
J.G.	69	M	AP + MI	2	80	I; W	0	abn	0	abn	0	Pos	−	290	0	B N	B high	G high	0
J.H.	54	M	AP	7	20	I	0	N	0	abn	I	Pos	0	222	0	B low	B high	A_2 slow	0
E.H.	57	M	AP	12	20	?	0	abn	I	abn	I	B	0	335	0	−	B high	N	0
G.H.	46	M	MI	6	20	0	0	N	0	N	I	Pos	I	244	0	B high	0	N	A_2 slow
E.K.	59	F	AP + MI	4	80–160	I	0	abn	0	abn	I	N	−	335	−70	B high	0	A_2 slow	0
J.L.	59	M	AP	22	20	I	† libido	abn	0	abn	0	Pos	0	265	0	−	−	−	−
C.L.	52	M	Per. vas.	2	20	0	0	N	0	B	0	Pos	0	217	+20	−	−	−	−
F.L.	58	F	AP	2	40	0	0	N	0	abn	W	−	−	290	−47	N	0	N	0
A.L.	62	M	AP + MI	15	20	I	0	abn	0	abn	I	Pos	0	317	+28	−	B high	−	A_2 slow
H.L.	50	M	AP + MI	13	20	I	0	abn	0	abn	0	Pos	0	185	+32	−	B high	−	−
O.M.	45	M	AP + MI	5	20	I	† libido	abn	0	N	0	Pos	I	345	0	N	A low	N	0
L.P.	43	M	AP + MI	12	20	I	0	abn	0	N	W	N	0	237	0	N	0	−	G high
F.R.	51	M	MI	13	20	0	0	abn	0	abn	I	Pos	I	258	0	N	B high	N	A_2 slow
E.K.	75	F	AP + MI	1	80	W	0	abn	0	abn	0	N	−	290	−33	N	0	G high	0
A.S.	60	M	AP	26	40	I	† libido	abn	I	N	I	−	−	280	−110	B high	−	A_2 slow	−
J.S.	63	M	AP + MI	9	20	I	0	abn	0	abn	0	B	I	280	0	B high	−	N	−
J.U.	62	M	AP	5	20	0	0	abn	0	abn	0	Pos	I	203	+27	B high	0	A_2 slow	N
J.W.	53	M	AP	3	80–160	0	0	B	I	B	W	−	−	210	+63	N	0	N	0

Abbreviations are the same as that used in Table 3, for Manvene. AP refers to angina pectoris, MI to myocardial infarction. In the Clinical Result column, as well as under ECG and BCG results, I indicates improvement, W worsening In all columns, 0 is used when no significant change occurred. The lipoprotein patterns are referred to as B for beta, A for alpha, and serum proteins abbreviated in the same manner. The notation "A_2 slow" refers to the retarded migration of alpha-2 globulin in the electrophoretic field. In all columns, N indicates normal, abn,. abnormal.

TABLE 2.—A SUMMARY OF THE MAJOR CHANGES NOTED DURING THE TEST PERIOD WITH SC 4289

	Clinical Status	*ECG*	*BCG*	*Cigarette Test*	*Cholesterol*	*Lipoproteins*
Improved	15 (65%)	5 (21.7%)	10 (43.5%)	6 (35.3%)	6 (26.1%)	2 (15.4%)
No change	7 (30%)	18 (78.3%)	9 (39.1%)	11 (64.7%)	9 (39.1%)	7 (53.8%)
Worse	1 (4%)	0 (0)	4 (17.4%)	0 (0)	8 (34.8%)	4 (30.8%)

anginal pain was striking in several patients.

No feminization occurred, and in 3 male subjects there was unquestioned increase in libido and potentia.

Objective studies were inconclusive, but of considerable interest: 21.7% showed electrocardiographic improvement, and 43.5% showed improvement in the ballistocardiogram; 35.3% demonstrated a less marked ballistocardiographic reaction to smoking. The most surprising observations concerned the serum lipid patterns. Although 26.1% showed a fall in total cholesterol, 34.8% showed an increase in level. It seems probable that no real change resulted, in view of the divergence of results. Electrophoretic patterns, in general, seemed to reflect an increase in the fraction of lipoprotein moving in the beta zone, with 4 patients changing from normal to high beta, 3 showing high beta values when control levels were not available, and only 2 showing a favorable change from high beta levels during the control period to normal during the drug test period. Serum protein changes seemed to be insignificant.

B. SC 6924 (MANVENE). Twenty-nine patients have received this drug, and results of therapy are available in 27 of these. Individual results are charted in Table 3, and a summary of changes is given in Table 4. Experience with Manvene is shorter, and the average patient exposure is 7.3 months. Subjective reactions to this agent differed qualitatively from that observed with SC 4289. The sense of "well-being" noted by the patients on SC 4289 was not felt, in general, by those receiving Manvene, and several complained of a vague sense of uneasiness, especially when the Manvene test period followed the SC 4289 period. Unpleasant sensations usually appeared in the early weeks of treatment, and tended to disappear subsequently. Despite this, and in the short treatment period reported, 73% noted some decrease in anginal pain, and in several subjects this relief was dramatic. In contrast to SC 4289, increasing duration of drug exposure seemed to produce greater subjective relief, an observation which is common in patients receiving conventional estrogens.

Objectively, the ballistocardiogram, the cigarette test, and total serum cholesterol were influenced during this period of therapy in a manner which is comparable to that noted with SC 4289. Improvement in ballistocardiographic form was found in 48.0%, 35% demonstrated an improved response to smoking, and 20.0% had a fall in total serum cholesterol. On the other hand, a trend toward reversal of serum lipoprotein distribution was detectable. In contrast to the effects of SC 4289, 65.0% showed a favorable shift in beta lipoproteins to or toward normal. Fifteen per cent showed the opposite change, a phenomenon which is difficult to explain in view of other evidences of estrogenicity found with Manvene. It seems similarly parodoxical that favorable lipoprotein shift often occurred with small daily dosage, and in some instances, relatively large quantities of this drug were ineffectual. Again, serum proteins were not affected in most subjects.

That some feminization occurred with Manvene is indisputable. On the other hand, only 2 male subjects complained of complete loss of potentia, and in both there was definite decrease of libido and potentia during the control period. Recovery from this effect was prompt in the one subject in whom sufficient time has elapsed to observe the effect of drug withdrawal. Minimal to moderate breast soreness and enlargement occurred in 55%, but in only one was this sufficiently objectionable to necessitate discontinuance of ther-

TABLE 3.—TABULAR SUMMARY OF THE EFFECTS OF MANVENE

Daily Clinical Estro- ECG

TABLE 3.—TABULAR SUMMARY OF THE EFFECTS OF MANVENE

Name	Age	Sex	Diagnosis	Mos. R	Daily Dose mg.	Clinical Result	Estrogen Effect	ECG Control	ECG Change	BCG Control	BCG Change	Cigarette Test Control	Cigarette Test Change	Cholesterol Control	Cholesterol Change	Lipoproteins Control	Lipoproteins Change	Serum Proteins Control	Serum Proteins Change
L.B.	56	F	MI	8	10–5	I	M,B	abn	0	abn	0	N	0	365	0	B high	—	A_2 slow	—
E.B.	55	M	AP + MI	15	10	–	–	abn	I	abn	I	–	–	345	−80	—	B N	—	N
N.A.	56	M	AP	9	20–10	0	B	N	0	abn	0	Pos	0	230	+68	B sl. high	B N	A_2 slow	A_2 N
M.B.	43	F	AP + MI	7	20	I	B	abn	0	abn	I	B	W	200	0	B high	B N	N	0
C.C.	55	M	AP	2	10	I	0	B	0	abn	0	N	–	250	−33	B high	B sl. high	G high	G.sl.high
J.C.	38	M	AP + MI	12	40–10	I	B	N	0	N	0	N	0	250	+85	B high	B sl. high	—	–
G.D.	61	M	AP	10	20–10	0	B	abn	0	N	0	N	–	256	0	B high	B low	N	0
V.F.	43	M	AP	3	10	I	0	N	0	N	I	Pos	I	325	0	—	—	–	–
J.H.	37	M	AP	2	20	I	0	N	0	B	0	B	0	210	0	N	B sl. high	N	G.sl.high
G.H.	46	M	AP + MI	5	20	I	B,LS	N	0	N	W	N	0	280	0	B high	B low	N	0
F.H.	60	M	AP	12	10	0	B	abn	0	abn	I	Pos	0	217	0	N (Estrogen)	0	N	0
A.H.	52	F	AP	11	20–10	I	B,M	abn	0	abn	I	N	0	190	0	N	0	N	0
W.K.	38	M	AP + MI	13	40–20	*I	B,LS	N	0	N	0	B	0	280	+65	B high	B N	N	0
E.K.	60	F	AP + MI	10	20–10	I	0	abn	0	abn	I	N	0	265	0	B high	0	N	0
C.K.	40	M	AP + MI	8	10	*I	BS	abn	I	B	I	Pos	I	230	0	B high	B N	N	0
J.L.	61	M	AP	8	10	*0	B,LS (0 with *)	abn	0	abn	I	Pos	I	273	0	B high	B N	N	0
											0	Pos	–	335	−132	B high	B sl. high	A slow	0
D.L.	48	F	MI	7	10	*0	0	abn	I	B									
J.L.	39	M	AP + MI	5	40–10	I	B	abn	0	B	0	B	–	273	0	B high	B N	N	0
A.L.	61	M	AP + MI	5	10	0	LC	abn	0	B	I	Pos	I	345	−55	B high	B sl. high	A_2 slow	0
H.L.	50	M	AP + MI	4	20	I	LS,B	abn	0	abn	I	Pos	I	217	0	B high	—	N	–
O.M.	45	M	AP + MI	6	5	I	0	abn	0	abn	0	N	0	265	+35	B high	0	N	0
J.M.	39	M	AP + MI	5	10	*I	0	abn	0	B	I	Pos	–	375	+35	—	—	–	–
L.R.	39	M	AP + MI	2	50–25	0	LC	abn	0	N	0	N	0	386	–	B h'gh	—	N	–
J.R.	40	M	AP + MI	12	25–10	I	LS,B	abn	I	N	0	N	0	273	+42	B N	B h'gh	N	A_2 slow
J.S.	42	M	AP	7	50–10	I	0	abn	I	abn	I	B	I	325	−75	B N	B sl. high	N	0
J.U.	62	M	AP	5	10–5	I	S	abn	–	abn	I	B	–	230	–	B high	—	N	–
J.V.H.	42	M	AP + MI	4	10	I	BS	N	0	N	0	Pos	I	265	+100	—	—	–	–

Estrogen effect is designated in the following manner: B = breast soreness or enlargement, LS = slight diminution in libido, LC = complete loss of libido and potentia, and S = gastrointestinal irritation. Other abbreviations are the same as those listed for Table 1. (*Nilevar 10 mg. daily was added.)

TABLE 4.—A SUMMARY OF THE MAJOR CHANGES NOTED DURING THE TEST PERIOD WITH MANVENE

	Clinical Status	ECG	BCG	Cigarette Test	Cholesterol	Lipoproteins
Improved	19 (73%)	5 (19%)	131 (48%)	7 (35%)	5 (20%)	13 (1 p Rx normal) (65%)
						2 high (nc) (20%)
No change	7 (27%)	21 (81%)	13 (48%)	12 (60%)	13 (52%)	2 normal (nc)
Worse	0 (0%)	0 (0%)	1 (4%)	1 (5%)	7 (28%)	3 (15%)

TABLE 5.—A SUMMARY OF THE MAJOR CHANGES NOTED DURING THE TEST PERIOD WITH CONVENTIONAL ESTROGENS

	Clinical Status	ECG	BCG	Cigarette Test	Cholesterol	Lipoproteins
Improved	9 (82%)	1 (10%)	11 (100%)	3 (60%)	6 (60%)	4 (50%)
No change	1 (died accident) (9%)	9 (90%)	—	2 (40%)	4 (Normal) (40%)	4 (Normal) (50%)
Worse	1 (died infarction) (9%)	—	—	—	—	—

apy. Gastrointestinal symptoms prohibited adequate dosage in one subject, and the daily dose was reduced in 2 women because of uterine bleeding.

C. CONVENTIONAL ESTROGENS. Our experience with conventional estrogens is severely limited. In all of 17 subjects given massive doses of estrogens (stilbestrol, Tace, or Premarin) evidence of estrogenicity was clearly apparent, especially in the men, all of whom noted a total loss of potentia. Uterine bleeding imposed a great handicap in the women. Adequate laboratory control and therapeutic observations are available in only 11 patients who tolerated larger doses of estrogen. Table 5 summarizes the changes during conventional estrogen therapy. Nine patients or 82%, were subjectively improved, during treatment periods ranging from 4 to 33 months (mean 14 months). Ballistocardiographic form improved in *all* subjects, including the 2 who died, 60% showed less deterioration of ballistic form in the smoking test during estrogen therapy. The lipid studies were consistent, in that 60% showed a cholesterol fall (to normal) and 40% were normal during the control period. Beta lipoproteins fell to normal in 50%, were normal in the remaining 50% in the control period. The mean cholesterol fall was 86 mg. per 100 ml.

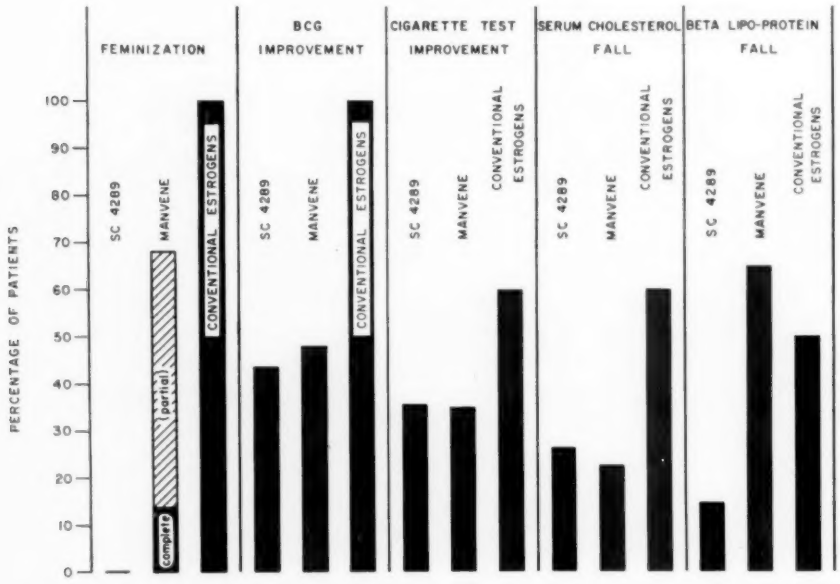


Fig. 2.—Comparison of the effects of SC 4289, Manvene, and ordinary estrogenic substances. Partial feminization, cross-hatched for Manvene, refers to breast soreness or incomplete loss of potentia, whereas the black bar for conventional estrogens and black portion of the Manvene bar refers to total loss of potentia in male subjects.

Figure 2 summarizes the comparative effects of the two new substances, SC 4289 and Manvene, as contrasted to ordinary estrogens.

Discussion. All attempts to reverse the relentless march of atherosclerosis are necessarily of experimental nature, and will remain so until more definitive

evidence allows a more direct attack on the specific metabolic defect responsible for this disorder. Detection of the presence of atheromata in the living human subject is possible only with surgical exposure of involved vessels, and presumptively, when angina pectoris recurrently manifests itself or myocardial infarction occurs. With present methods, objective appraisal of *alteration* of the atherosclerotic lesion presents even more insurmountable difficulty. It is with this realization that these studies were performed, as part of a long-range, multifaceted study of coronary artery disease. It is likewise because of this realization that several divergent methods of evaluation were utilized.

It should be emphasized that subjective changes must be appraised with great caution. The susceptibility of patients with angina pectoris to placebo therapy is all too well recognized to need repetition here. Subjective reaction is included only as a facet of the over-all response to these agents, and no conclusions drawn as to their significance. It seems possible that the high incidence of improved sense of well-being noted with SC 4289 *may* reflect an androgenic rather than estrogenic effect. On the other hand, our experience with conventional estrogens, in doses greatly exceeding those customarily used, has demonstrated that during many months of therapy there is almost always clinical improvement, as judged by daily nitroglycerine consumption.

The significance of electrocardiographic and ballistocardiographic improvement, although difficult to appraise in relatively short term studies, is greater than that of subjective changes. The 21.7% of patients showing electrocardiographic improvement while on SC 4289, and 19.0% improving on Manvene would seem of potential significance, especially since none showed worsening during the test periods. The improvement usually was in the ST–T, a portion of the electrocardiogram which is subject to many influences. Our experience with the ballistocardiogram has shown that spontaneous improvement in the untreated patient with coronary artery disease (excluding acute myocardial infarction) occurs in approximately 6.5% of patients, during a period of 2 years. The 43.5% improvement in patients treated with SC 4289, and 48.0% in those given Manvene suggest the possibility of true objective benefit, although these figures were not subjected to statistical analysis because of the many variables involved. Chief among these variables was the fact that general measures were usually being enforced during control and test periods, and many were receiving diets low in fat. The latter especially complicates evaluation of drug effect, since 30% of our patients adhering closely to a low fat diet for one year or more have shown ballistocardiographic improvement[11]. As was mentioned above, efforts were made in most instances to continue the dietary program on which each patient had been maintained during the control period, but even this would not prevent the added beneficial effect of rigid fat restriction from becoming manifest during the drug test period. The short test period, especially with Manvene, would seem to minimize the likelihood of this. At this stage of our studies, sweeping conclusions as to the effects of these drugs on the ballistocardiogram and electrocardiogram do not seem warranted. It should be noted that 100% of our subjects receiving massive doses of conventional estrogen have shown some ballistocardiographic improvement, but the duration of therapy with these drugs exceeds the test periods with the currently reported agents.

The greatest significance seems to lie in the effects of SC 4289 and Manvene on the serum lipid levels. Total cholesterol values were not changed significantly, although in our experience, as well as that of Barr[2], the total cholesterol can be reduced with conventional estrogens. The failure of SC 4289 to effect a favorable (estrogenic) shift of the lipoprotein distribution leads to the conclusion that this compound is not desirable in the metabolic approach to the treatment of atherosclerosis. Manvene, on the other hand, produced a favorable shift from high beta-lipoprotein levels to normal in 65% of patients, and another 10% had normal control values. This result is comparable to our experience with conventional estrogens, with which all sera have reverted to normal pattern or had normal control values (when massive doses were tolerated), but the unpleasant side effects are far less dramatic with Manvene. All male patients, in this series, lost their potentia completely when treated with ordinary estrogenic substances, whereas this occurred in only 12% during Manvene therapy. Breast changes, although present in 55.5% of those treated with Manvene were not as objectionable as with the customary estrogens. In the patients given Nilevar and Manvene, the breast changes could be reversed by doses which did not influence serum lipids, although when libido and potentia were normalized, the serum lipid improvement was no longer maintained. It must be clearly admitted that no real proof is available which allows the conclusion that a shift of lipoprotein distribution from preponderant beta to preponderant alpha is beneficial therapeutically in human subjects with established coronary atherosclerosis. Despite the theoretical nature of these efforts, until other indices toward which to direct our efforts become apparent, it seems reasonable to attempt such reversion in a select group of experimental patients. To make such efforts practical, feminization of the male and uterine bleeding in the female must be minimized. Such a possibility exists with the second of the two compounds reported, namely, Manvene. This effect may well prove to be attainable in only a fraction of all patients, but at the present time the optimal dosage has yet to be determined, and efforts are under way to exhibit a weak androgenic substance (Nilevar) with larger doses of Manvene to achieve greater lipid effects, and still avoid feminization. It would be preferable to attain greater estrogenic effect on the lipids than was obtained in the present studies, especially with regard to the total serum cholesterol, although this may not be possible without prohibitive side effects. Failure to lower total serum cholesterol, even with massive doses of estrogen, has been reported by Gertler, Hudson and Jost[4]. In their experience the phospholipid level rose, leading to a more normal cholesterol:phosphoslipid ratio. This pattern of response was noted in the chick (Pick *et al.*[6]).

The only other experience with Manvene which has been reported is that of Robinson, Cohen and Higano[7], whose studies would similarly indicate the possibility of serum lipid activity without inordinate estrogen side effects. These workers exhibited larger dosage (50 mg. daily), and after 8 weeks, 7 of 12 men showed no estrogenic side effects, despite favorable lipid shifts. Our experience would indicate that longer periods of observation are necessary, since side effects have often not occurred until about the eighth week of exposure, and most of our subjects have not tolerated doses exceeding 10 to 20 mg. daily over 2 months.

It is clearly recognized that "favorable" lipoprotein shifts, obtainable in most patients with Manvene with minimal feminization, and in all patients given ordinary estrogen in doses sufficient to elicit definite feminization, might represent a goal which could be attained with smaller doses of certain other estrogenic materials. Our experience with small numbers of patients given doses of stilbestrol in the order of 1 to 3 mg. daily suggests that this dosage will not produce a lipoprotein alteration to the young female pattern. A graded dose-response curve in large numbers of patients cannot be reported with our limited experience. It is also certain that Manvene is not the ideal drug, since lipid activity is not obtainable without detectable feminization. Whether such an ideal drug, of steroidal structure, can be designed, remains to be determined.

Conclusions. Preliminary observations of the effects of two new compounds in patients with coronary atherosclerosis are reported and compared to the actions of conventional estrogenic substances. The premise that the young female pattern of serum lipoprotein distribution is desirable was tentatively accepted, and efforts to attain this pattern without undue feminization were made. Such effects were accomplished in 65% of patients treated with one of the two compounds (Manvene) although 15% paradoxically showed the opposite effect. Other evidences of objective improvement were not definitely established, although some suggestion of electrocardiographic and ballistocardiographic improvement, especially the latter, over and above that expected in untreated patients, was noted. From these relatively short term observations it would seem that the possibility of extended therapy with Manvene, in quantity sufficient to favorably influence serum lipids (and possibly other objective measurements) exists, with prohibitive feminization occurring in far fewer patients than appears during ordinary estrogen treatment. It should be strongly emphasized that this form of treatment is experimental, and should not be indiscriminately applied in the care of patients with coronary atherosclerosis until more definitive *human* evidence is available.

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(Interlingua on page 78)

DIFFUSE INTERSTITIAL PULMONARY FIBROSIS (HAMMAN-RICH SYNDROME) IN AN ALLERGIC PATIENT: REPORT OF A CASE*

By Louis Tuft, M.D.
CLINICAL PROFESSOR OF MEDICINE

AND

Leonard S. Girsh, M.D.
INSTRUCTOR IN MEDICINE

(From the Allergy Clinic, Temple University Hospital and Medical School, Philadelphia, Pennsylvania)

The case being reported is one of diffuse interstitial pulmonary fibrosis diagnosed antemortem by lung biopsy and successfully treated with long term cortisone therapy. This condition was first described in 1935 (Hamman and Rich[3]) as a fatal pulmonary disease of unknown etiology and is now known as the "Hamman-Rich syndrome." Since then a total of 40 cases of interstitial pulmonary fibrosis of the Hamman-Rich type have been collected, according to Grant, Hillis, and Davidson[2], who published an excellent review of this disease in October, 1956, when they reported 3 additional cases. Originally the diagnosis was established after death and only after careful microscopic studies. But in 3 recent cases, diagnosis was made antemortem by lung biopsy. This permitted earlier institution of treatment and in 2 cases a more favorable therapeutic response. Thus, the patient reported by Pinney and Harris[4] in February, 1956, remained clinically well after 17 months of cortisone therapy, and thus far, our patient is still living after 20 months of prednisone therapy .

Case Report. The patient, Mrs. I.M., age 44, was first seen on November 8, 1955, with the chief complaint of cough, dyspnea, and fatigue.

Except for occasional head colds, noted especially in the spring, the patient was in very good health; in fact, she was a track and swimming star during her high school days. She rarely saw a physician, except for an appendectomy in 1943, and for the removal of cysts from her breast in 1948. She remained well until May, 1953, when she first noted her menstrual periods were irregular, and she had a feeling of fatigue which necessitated her giving up her job in August, 1953. At that time her weight was 142 pounds. Following this, however, there was a progressive weight loss during the next 8 months, and because of irregular menses she was given tablets of Sulestrex (an estrogenic hormone with the chemical formula of piperazine-estrone-sulfate) which she took in a dosage of 1.25 mg. daily from June, 1953, to October, 1954; also phenobarbital, ½ grain four times daily for a shorter period.

On March 27, 1954, the patient complained of tiredness and urinary symptoms, frequency and nocturia with pus cells present in her urine. For this she was given two tablets of Gantrisin (0.5) every 4 hours until April 3, 1954, at which time they were discontinued because the patient was symptom-free and the urine examination was negative.

On June 1, 1954, she developed what was diagnosed as "virus pneumonia" characterized by sore throat, generalized aching, chills, marked fatigue, weight loss (from 134 to 129 pounds), and a severe cough resembling whooping cough but productive of only some white mucoid sputum. There was slight fever and pain in the left side of the chest. Roentgenogram of the chest taken June 3, 1954, was reported as follows: "There is a good deal of inflammatory reaction throughout both

*Presented before the Section on Medicine of the College of Physicians of Philadelphia, April 22, 1957.

lungs involving especially the bases and the right intraclavicular area. This is probably all due to virus pneumonitis but an opinion concerning the possibility of underlying tuberculosis in the upper lobes must be reserved until a later date. Heart is not enlarged." She was given 250 mg. Aureomycin every 6 hours for a period of 3 weeks but had to discontinue the drug because of severe diarrhea. Another chest roentgenogram was done June 22, 1954 with the following report: "The appearance of the lung fields has not improved since June 3, 1954, but there is no extension of the process. Appearance of chest certainly suggests an inflammatory process but the exact etiology is not clear from the roentgenographic examination. The possibility of underlying fibrosis from asbestos inhalation or less likely one of the collagen diseases might be considered." Tuberculin skin tests were negative.

Following this attack, despite ingestion of multiple vitamins, she continued to be tired, lost considerable weight, and on October 20, 1954, was admitted to the Lancaster General Hospital for study. Most of the studies were negative with the exception of the chest roentgenogram done November 26, 1954, which showed very little change in the abnormal infiltration in the lung fields. The patient was told her chest looked as though she had worked in an asbestos plant. She was admitted to the same hospital January 5, 1955, at which time the radiologists reported that, "The diffuse infiltration in the upper lobes is a little more extensive than in June. In the bases, these infiltrations appear to be somewhat conglomerate and, I believe, have not changed materially." A diagnosis of Boeck's sarcoid was considered and the patient was given hydrocortisone for a short period, but without benefit.

In January, 1955, she started to take Ambodryl, and noted some improvement. However, she continued to have dyspnea, cough, and congestion in the chest. In May, 1955, she had another episode of so-called "virus pneumonia" which was similar to the attack in 1954, but more severe. At that time, too, she had only a slight fever. She again received antibiotic therapy (Aureomycin), but did not tolerate this drug very well and continued to complain of increasing dyspnea, cough, and fatigue. Dyspnea was noticeable on exertion, especially going upstairs. Allergy studies were suggested at that time; but since she was about to move to Chester, she decided to wait until the fall to have this done.

When first seen at the office of the senior author in late November, 1955, she complained of dyspnea, cough, and questionable wheezing. There also was a history of severe attacks of nasal difficulty diagnosed as "sinus infection," recurring especially in the spring, off and on for about 15 years. She also had several bouts of hives attributed to strawberries, and diarrhea induced by the ingestion of pork. She could not tolerate tobacco nor any type of perfume. At one time the patient was a prolific smoker, but she gradually developed an intense dislike to being near anyone who smoked, and has not smoked for more than a year. She now could not tolerate the inhalation of even the slightest amount of tobacco smoke.

The family history was strongly positive for allergy, her mother having had rose fever, and several nieces and nephews having hives.

PHYSICAL EXAMINATION at the initial visit revealed the following:

The patient's weight was 104 pounds and the blood pressure 106/70. There was slight pallor of the nasal mucous membrane, some clubbing and cyanosis of the finger tips and slight increase in breath sounds and some subcrepitant rales in the right scapular region posteriorly. Fluoroscopic examination showed moderate increase in the hilar shadows and vascular markings throughout the lungs.

Intracutaneous skin tests showed no significant reactions except to house dust. Ophthalmic tests were positive to ragweed and to tobacco.

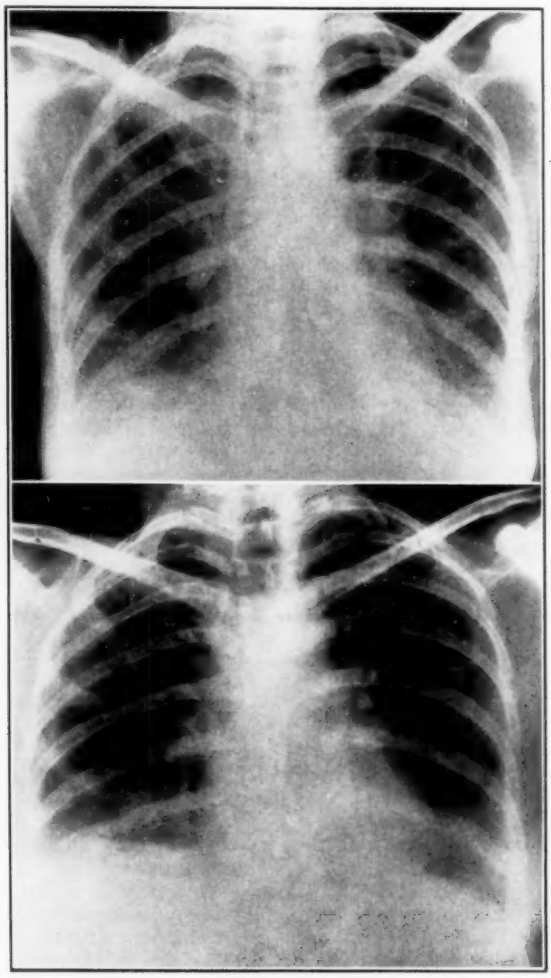
She was treated symptomatically during the course of the allergy studies, but without improvement. During December her condition grew progressively worse; and she was admitted to Temple University Hospital on January 3, 1956, because of increasing fatigue, slight rise in temperature, rapid pulse, dyspnea, and pain in the right scapular region. Examination shortly after admission revealed evidence of marked weight loss (from her normal weight of 140 to 104 lbs.), slight temperature rise as well as the clubbing and cyanosis of the fingers, and similar abnormal physical signs in the right scapular region to that previously noted.

Roentgenogram of the chest taken January 4, 1956, was reported as follows: "There are disseminated uniformly distributed coarsely granular and nodular densities against a fine honeycomb of interstitial reticular pattern extending out to the periphery of both lungs. The hilar shadows are poorly defined as a result of the adjacent abnormal lung densities. The heart is of normal size and contour. Various diagnoses are suggested as possibilities including Boeck's sarcoid, reticuloendo-

theliosis, and the Hamman-Rich syndrome" (see Fig. 1A).

Roentgenogram of the long bones for evidence of Boeck's sarcoid showed them to be completely normal. Roentgen-ray study of the accessory nasal sinuses showed them all to be normal except for mucous membrane thickening and probable mucocele in the right maxillary antrum. Laboratory tests, including urine analysis, blood count, serology and blood culture and sputum for acid-fast organisms, were all negative, except for an eosinophil count of 5% which was the same as reported in her hospital stay in Lancaster. Agglutination tests for typhoid, paratyphoid, and brucella also were negative. Skin tests

A



B

Fig. 1A.—*Chest roentgenogram:* Prior to treatment, Jan. 4, 1956, revealing diffuse interstitial pulmonary fibrosis and uniformly distributed nodular extradensities.

Fig. 1B.—*Chest roentgenogram:* After treatment, April 11, 1957, revealing definite improvement in diffuse fibrosis and nodular densities.

were negative for coccidioidomycosis, histoplasmosis and tuberculosis.

Pulmonary function studies done on January 10, 1956, by external spirometry showed slight reduction in the breathing reserve (to 84%) and moderate reduction in the vital capacity, which was 1300 ml. (normal 2500 to 4000 ml.).

Because of the uncertainty in diagnosis, it was decided to do a lung biopsy. On January 13, 1956, under local anesthesia (paravertebral thoracic nerve block) a small section of the right upper lobe was removed for histological examination. The specimen grossly was firm to palpation. Microscopic examination was reported as follows: "The lung tissue is atelectatic with collapse of alveolar spaces, and with alveolar septal thickening due to fibrous tissue proliferation. The fibrosis occurs diffusely being largely septal and peribronchial. The alveolar spaces are lined by few cuboidal cells and contain numerous pale lipid-laden macrophages, some of which have fused to form giant cells (Fig. 2).

The small bronchi are normal and bronchiectasis is absent. No granulomata of tuberculosis or sarcoidosis are seen. There is no evidence of collagen disease of the vessels. Histologic diagnosis is: Interstitial pulmonary fibrosis."

Following the operation, the patient was given an injection of penicillin with immediate dyspnea and cyanosis requiring epinephrine and Demerol for relief.

Because of the history of intolerance to antibiotics and to cortisone, it was decided that the patient be given PABA (para-aminobenzoic acid). This was started on January 15, shortly before the patient was discharged from the hospital. She seemed slightly improved for a few days while on the PABA, but this was temporary, and the drug was discontinued at the end of a week. The condition progressed; and when seen on February 16, her condition had worsened. She had lost more weight (her weight being 93½ lbs.), her pulse was more rapid, and rales were audible at both bases.

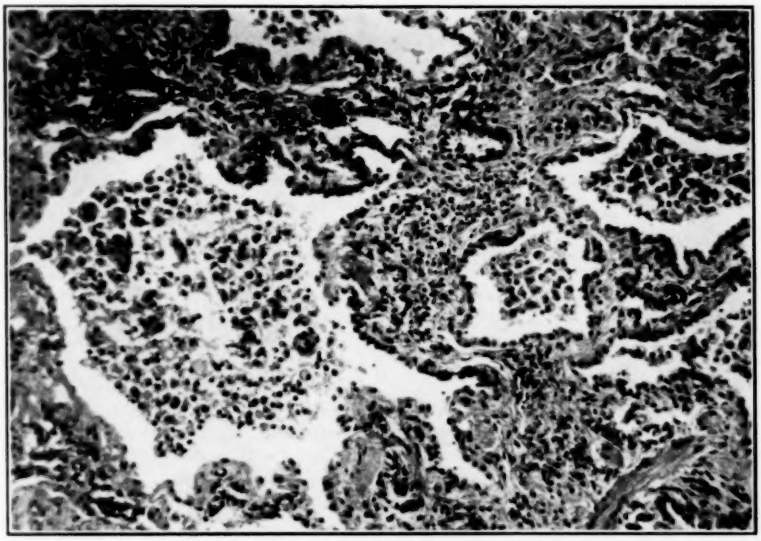


Fig. 2.—Lung biopsy revealing interstitial pulmonary fibrosis with alveolar septal thickening due to fibrous tissue proliferation, and alveolar spaces are lined by cuboidal cells and contain lipid laden macrophages and giant cells.

The patient was again hospitalized at Temple University Hospital on February 20, 1956. Examination now showed marked dyspnea, rapid pulse, cyanosis, and gallop rhythm with evidence of cardiac insufficiency. An electrocardiogram done on February 24, 1956, revealed the following: "Sinus tachycardia, rate of 125; electrically vertical heart with clockwise rotation; probable myocardial

disease probably secondary to pulmonary disease; marked respiratory variation of Q.R.S."

Another chest roentgenogram revealed the same findings as before. The blood count was normal except for 6% eosinphils. Other laboratory studies including sputum examination for tubercle bacilli were negative. There was slight reduction of plasma CO_2 to 47 volumes % (normal 50 to 75). Pulmonary function tests again revealed little change in the ventilatory function but definite lowering in the oxygen-combining power of the blood. (Arterial oxygen saturation was 69% and CO_2 content 43.7 volumes %).

Shortly after admission, the patient was digitalized, and after 2 days was given Meticorten (20 mg. daily) and a maintenance dose of 0.1 gm. Digifolin daily. Following this, she began to show striking improvement in her symptoms. Her appetite was better, there was definite decrease in her dyspnea, and for the first time she regained some of the weight she had lost (101 pounds). This improvement continued not only until the time of her discharge on March 3, 1956, but also subsequently. She continued to take Meticorten in dosages of 5 mg. four times daily and 0.1 gm. Digifolin once daily and was started upon ragweed pollen desensitization and injections of small doses of histamine subcutaneously. In addition she was instructed to avoid as much as possible any contact with house dust, tobacco smoke and irritating ordors. Upon this regimen, the patient showed continued and progressive improvement. Her weight increased slowly until it became more or less stabilized between 118 and 120 lbs. by October, 1956. She felt generally stronger but still had slight dyspnea upon moderate exertion and at such times became slightly cyanotic. On May 27, 1956, she again had an attack of pharyngitis and tracheobronchitis similar to those she had at about the same period back in 1954 and in 1955, and which had been diagnosed as "virus infection." She was given Terramycin (250 mg. q.i.d.) until July 15, 1956, with no untoward effects and with disappearance of the respiratory symptoms. During the ragweed hay fever season, she had mild sneezing, cough, and occasional wheezing which were easily controlled by administration of Ambodryl. She continued to have some dyspnea, pain in the chest, and cough upon exertion and especially after unavoidable inhalation of tobacco smoke or exposure to inclement weather. These attacks usually were controlled by administration of Terramycin and, when necessary Ambodryl and codeine and elixir terpin hydrate. To prevent the onset of upper respiratory infections, the patient took a single dose of Terramycin (100 mg.) daily throughout the winter, this being increased in amount and frequency whenever necessary.

In order to determine the extent of her improvement, repeat pulmonary function tests and chest roentgenogram were done on October 3, 1956. The latter was reported as follows: "Once again we note a diffuse punctate type of density throughout the lung fields, in the category of nonspecific interstitial fibrosis. We gain the distinct impression that some improvement has occurred since our previous examination of 8 months ago. Although the present film shows slight increased penetration compared with the previous study, we nevertheless believe that the abnormal pattern of pulmonary architecture is not as conspicuous due to some diminution in caliber of the abnormal densities."

The pulmonary function studies showed little change in the ventilatory function but striking improvement in the arterial oxygen (from 69% to 92%).

Since October, 1956, the patient's condition has been more or less stationary. She has had only minor respiratory symptoms readily controlled by symptomatic measures. In January, 1957, she began to show slight evidence of hirsutism from the Meticorten therapy. An attempt, therefore, was made to reduce the Meticorten gradually so that at present she is taking 12.5 mg. to 15.0 mg. divided into three doses daily in addition to 0.1 gm. Digifolin and 100 mg. Terramycin daily. When last seen her weight was 121 lbs.; no rales were audible in the chest and except for slight dyspnea on exertion, she is quite comfortable.

Repeat chest roentgenogram done April 11, 1957, showed the same general changes as noted in October, 1956, but even after making due allowance for slight differences in the technique of exposures, it was felt that the slight but definite improvement previously noted has been maintained (Fig. 1*B*).

Repeat pulmonary function tests done at the same time showed no change in the ventilatory function but there still was an increase in arterial oxygen saturation from the original 69% to 94%.

Discussion. From the clinical data presented, supplemented by radiologic evidence and confirmed by histologic examination of a biopsy specimen of the affected lung tissue removed surgically, there seems little doubt that

the patient herein reported has the uncommon condition of diffuse pulmonary fibrosis designated as the Hamman-Rich syndrome. Without the conclusive evidence of the lung biopsy, clinical diagnosis of this syndrome is difficult; in fact, in all but 2 of the reported cases it was made postmortem. This might have been true in the present case if reliance were placed solely upon Roentgen-ray examination of the chest, which presented a picture that resembled sarcoidosis, pneumoconiosis (asbestosis) or tuberculosis. These possibilities were excluded by the histologic examination. Furthermore, the absence of known contact with beryllium and failure to demonstrate it by polariscopic examination of the histologic section probably excludes berylliosis.

The etiology of this syndrome still remains obscure. Hamman and Rich[3] originally suggested drug allergy as a possible cause, since one and perhaps a second of their 4 cases had received arsphenamine prior to the onset of the disease. Their contention is supported somewhat by the fact that of the total of 40 cases previously reported, 14 had positive antecedent histories of the administration of potent drugs capable of inducing allergic sensitization. In 8 of those, symptoms of the disease appeared 4 to 12 months after treatment with hexamethonium and Apresoline. Both these drugs have been known to induce in other patients a picture of acute rheumatoid arthritis and a lupus-erythematosus-like picture. Two patients had a history of previous administration of sulfa, one received penicillin, and one streptomycin. Another patient received both penicillin and streptomycin, and the final case, that reported by Hamman-Rich, arsphenamine. No mention is made in 17 other patients of the possibility of previous drug administration, although some of these patients might have received such drugs. And in the remaining 6, it is definitely stated that no known drugs were given prior to the onset of the disease.

In our own patient, it is difficult to establish drug allergy as the cause of her symptoms. Although she herself was allergic and, therefore, was more susceptible to sensitization, the only drug which she took for any length of time was the estrogenic hormone, Sulestrex, which is a poor sensitizer. Furthermore, at the time this drug was given for symptoms attributed to menstrual irregularities, she actually might have been showing the early symptoms of her disease. She also took Gantrisin and Aureomycin but only for short periods and after her disease had become evident, so that these can be excluded. There still remains one possible factor in her etiology which recently came to our attention. Chamberlin, Jennings, and Lieben[1] recently reported their findings in 20 cases of berylliosis developing in 11 patients with known exposure to beryllium and in 9 others who though not directly exposed, lived in the vicinity of a beryllium factory in Reading, Pa. The symptoms in those patients were so similar to those of our own patient that we questioned her regarding possible beryllium contact. This could be excluded but she did tell us that from the time she moved to Lancaster in 1951 until she left in 1955, she was constantly bothered by the inhalation of an irritating odor present in the atmosphere in the vicinity of a linoleum factory. This bothered her just as much or even worse than tobacco smoke, but did not affect either her husband or other people in the same area. Subsequent inquiry from responsible authorities revealed the fact that the odor was the result of formation of irritant fumes given off from the oxidation of hot

linseed oil used in the preparation of the linoleum. These fumes seldom affected the workers or other people living in homes in the vicinity of the factory. Whether inhalation of these irritating vapors was sufficient to induce the progressive pulmonary fibrosis present in our patient is problematical and difficult to prove. But it is a possibility which cannot be dismissed entirely when one is concerned with a disease whose etiology is unknown.

Because many of the reported cases had one or more repeated viral pneumonia-like episodes, as did our patient, the possibility that this disease is due to a virus has been suggested. But except for the clinical symptoms, there is nothing else to substantiate a viral etiology.

Another interesting feature in this patient was the favorable response to long-term prednisone therapy. This has not been true of all cases treated with the steroids. Thus, since 1952, 10 patients with this disease have been treated for varied periods with the corticosteroids. Only two have responded favorably, our own case is still living after 14 months of continued prednisone treatment (20 mg. daily) and the case of Pinney and Harris after 17 months of cortisone (50 mg. daily). The treatment failed in the other 8 either because it was administered too late (as in 3 in whom the fibrosis was too advanced for the steroids to be beneficial), or the patient already was in cardiac failure. In others, the patient died either immediately after the steroids were discontinued or some days later. In retrospect, from a review of the experience of others with steroid therapy and in this patient, it would appear that best results will be achieved if the steroids are administered as early as possible in the course of the disease and for an indefinite period; also that their administration should never be discontinued abruptly, if at all.

Summary. We have presented a case of diffuse interstitial pulmonary fibrosis (known as the Hamman-Rich syndrome), confirmed by lung biopsy and occurring in a patient with a personal and family history of allergy. Continued prednisone therapy for a period of 20 months has resulted in marked symptomatic relief with coincident improvement in arterial oxygen saturation and slight, although definite, improvement in the roentgenographic picture. The possibility that this disease might represent a reaction of drug allergy has been considered but could not be substantiated in our patient; however, the patient has a history of continued inhalation of irritating fumes for a period of at least 2 years prior to the onset of her symptoms which must be considered as a possible etiologic factor in such a susceptible patient.

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(Interlingua on page 78)

THE RESULTS OF TREATMENT OF PSYCHOTIC STATES WITH NEWER PHENOTHIAZINE COMPOUNDS EFFECTIVE IN SMALL DOSES*

By Douglas Goldman, M.D.

(From Longview State Hospital, Cincinnati, Ohio; R. A. Haines, M.D., Superintendent)

The first American reports of the treatment of psychoses with drugs by Lehmann and Hanrahan[8], by Kinross-Wright[6], and by Kline[7], appeared in 1954. In the intervening 3 years, there has been a surge of activity, the like of which has not previously been felt in psychiatry. The therapeutic revolution of the 1930's initiated by the introduction of insulin, Metrazol, and later electroshock therapy and psychosurgery, was minuscule by comparison.

Foremost among the substances used in the treatment of psychotic states, have been the derivatives of phenothiazine; the most important and successful of which, until now, has been chlorpromazine (Thorazine); and reserpine, the chief active substance in the roots of various Rauwolfia species, which has generally been found useful but less dramatically effective.

The production of undesirable side-effects and the rare but significant occurrence of toxic changes from administration of chlorpromazine, particularly jaundice and agranulocytosis, have led to the search for compounds with similar therapeutic effect but less toxicity. Promethazine (Phenergan), promazine (Sparine), mepazine (Pacatal) and other phenothiazine compounds have been introduced as possible therapeutic agents for psychoses, but have not found the wide acceptance thus far achieved by chlorpromazine, chiefly because of their narrower therapeutic range and equal or greater toxicity. Recently, a number of phenothiazine derivatives effective in a much lower dose range than chlorpromazine have been studied. The present report deals with our experience with four of these compounds in the last 7 to 18 months. As a practical matter, I shall use the trade names in further discussion.

Compazine (proclorperazine) has been under investigation the longest and is represented by the largest number of patients. Trilafon and Vesprin have been under investigation for about 11 months, and represent a somewhat smaller experience. Winthrop #13,-645–5 has been on trial for about 7 months and has indicated a definite level of usefulness, but in what might be called an introductory number of patients. Figure 1 represents structural formulas of the substances under consideration and familiar compounds for comparison. It is noted that Compazine and Trilafon are quite similar in structure except for the presence of the methyl group in Compazine and an ethyl group in Trilafon. Vesprin is similar to Thorazine except for the substitution of a tri-fluoro methyl group for the chlorine. Winthrop #13,645–5 is characterized by the presence of a

*The drugs used in this study were supplied gratis by the manufacturers: Compazine by Smith, Kline & French Laboratories; Vesprin by E. R. Squibb & Sons; Trilafon by Schering Corporation; and Winthrop #13,645–5 by Winthrop Laboratories. We wish to express our gratitude for their generosity and assistance.

tropic acid complex at the end of the side chain of the phenothiazine ring. It is interesting to indicate that in spite of the fact that these substances are all of somewhat greater molecular weight than chlorpromazine, their dosage range is much smaller and the

to restrict any drug to any one ward or group of wards; ward management of the dosage was carried out through the drug treatment team meeting weekly as it is for all drugs in use or under investigation. Rating of results was strictly according to the scheme

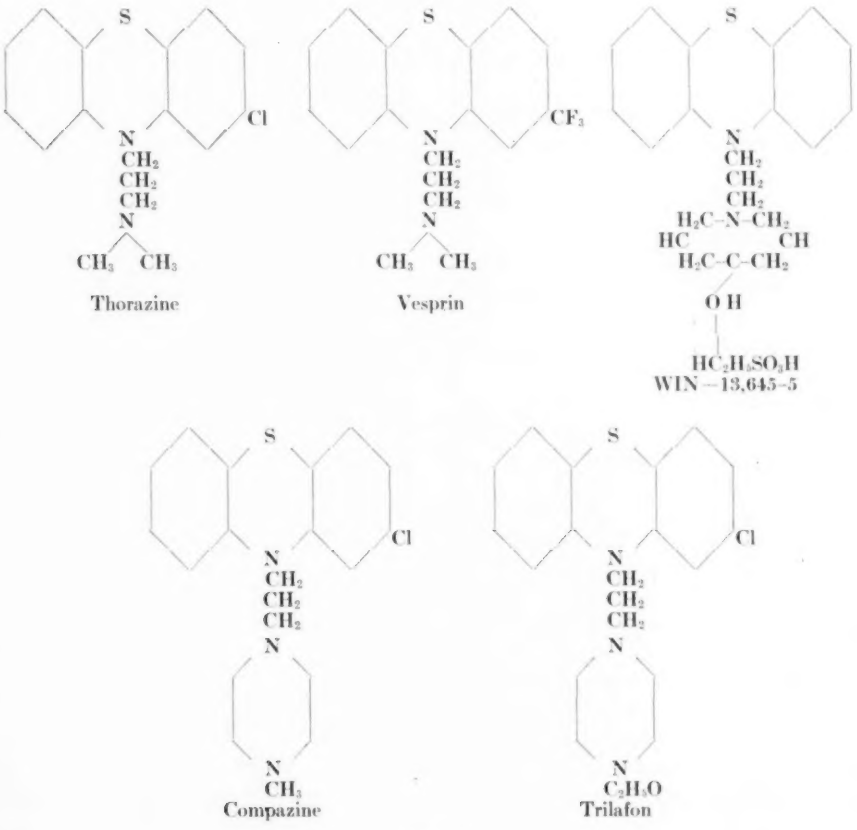

Fig. 1.

molar dose proportionately even smaller.

All of the patients studied were inpatients at Longview State Hospital in Cincinnati, Ohio. Patients were chosen at random from among those already hospitalized, and in a roughly alternating manner from the newly admitted group. No attempt was made

outlined in the legend to Table 6 with a number of physicians and nurses participating.

The dose range of the four compounds under consideration, with chlorpromazine for comparison, is indicated in Table 1. This table represents a survey of dosage distribution on a single day in Longview State Hospital.

TABLE 1.—DOSAGE

ORAL DOSES PER DAY

Thorazine	*No. of Pts.*	*Vesprin*	*No. of Pts.*	*Compazine*	*No. of Pts.*	*Trilafon*	*No. of Pts.*	*Winthrop #13,645-5*	*No. of Pts.*
mg./day		*mg./day*		*mg./day*		*mg./day*		*mg./day*	
Up to 50	49 4.2%	Up to 75	47 29.9%	Up to 25	27 5.0%	Up to 16	47 25.7%	Up to 25	5 5.7%
51–100	159 13.6%	76–150	59 37.6%	26–75	407 76.3%	17–32	70 38.2%	26–75	70 79.5%
101–300	333 28.6%	151–300	47 29.9%	76–150	91 17.1%	33–64	40 21.9%	76–150	11 12.5%
Over 300	627 53.7%	Over 300	4 2.5%	Over 150	9 1.7%	Over 64	26 14.2%	Over 150	2 2.3%
Total pts.	1168		157		534		183		88

Intramuscular Dose Per Injection, mg. (q. 4 to 8 hours)

50–200	25–50	10–20	5–20	5–50	

It is immediately apparent that among the patients receiving chlorpromazine, the majority receive more than 300 mg. per day. The majority of patients receiving Compazine, received less than 150 mg. per day. The majority of those receiving Trilafon received less than 65 mg. per day. With Vesprin, most received less than 300 mg. per day. With Winthrop #13,645–5, most have received less than 150 mg. per day. The intramuscular route shows similar proportionate differences. It is interesting that all of these substances are less

irritating on intramuscular injection than chlorpromazine and, therefore, permit administration of the full effective dosage intramuscularly. This has not been true of chlorpromazine because of the irritation produced by the injectable material.

Previous extensive and detailed experience with chlorpromazine in the treatment of psychotic states fortunately served as the background for evaluating these new and intensely active compounds. Without this background, the effects of these drugs in the initially recommended dose ranges would undoubtedly have led to abandonment of some or all of them. It is important to emphasize that these are potent substances recommended for treatment of severe illness. Since dose ranges vary rather widely for individual patients, it is important to establish each individual patient's effective dose in a conservative and deliberate manner so that unpleasant side-effects and toxicity can be avoided. Studies of the clinically important and recognizable effects of these drugs are outlined in Tables 2 to 5a.

TABLE 2.—ALLERGY-LIKE MANIFESTATIONS

	Thorazine	*Compazine*	*Trilafon*	*Vesprin*	*Winthrop #13,645–5*
Number of patients	1777	667	206	176	94
Rash	117	7	1	2	4
Edema	85	17	1	1	3
"Nasal stuffiness"	6	3	2	0	4
Asthma	2	1	1	0	0

Table 2 shows the proportion of patients developing allergy-like manifestations from administration of these drugs. It is immediately evident that the dermatologic reactions for Compazine, Trilafon and Vesprin are much less frequent than with chlorpromazine. The reactions from Winthrop #13,645–5 are only somewhat less frequent than those from chlorpromazine. It is noteworthy that such reactions occur only at the higher dose levels and probably can be practically eliminated by starting with relatively low doses and increasing slowly to an effective dose rather than by starting at the highest dose range and diminishing to an acceptable level. The respiratory symptoms are of less importance with phenothiazine compounds than with reserpine. All allergic manifestations are manageable by moderation of dosage or discontinuing the drug for a few days, administering as indicated antihistamines, and in the severest reactions, by the use of adrenocorticotropic hormone. In these tables, only those reactions requiring special attention and management are recorded. Minor reactions of this type do not require any modification of therapy since they are generally transient.

The earliest observations on the use of chlorpromazine all emphasized the sedative and even hypnotic effect of this substance. It is this effect which led to the general use of the term "tranquilizer." It is immediately evident, however, that the production of somnolence by these newer compounds is much less frequent and, a fact not indicated in Table 3 by mere numbers, much less intense than that produced by chlorpromazine. Winthrop #13,-645–5 is the possible exception to this statement in that with larger doses it does produce an important degree of

sedation. The important beneficial effect on psychotic symptoms, resolution of delirium, hallucinations and delusions, can in most patients be achieved with Compazine, Trilafon or Vesprin with practically no sedative effect, and in some patients with what is unquestionably actual stimulation, particularly with Compazine and Trilafon. This "stimulating" effect sometimes is excessive and leads to what has been called "turbulence" or "tension state." This effect has been noted with reserpine by Barsa and Kline[2] and has been reported as a side-effect with the use of Trilafon by Ayd[1] and by me previously with Compazine[5]. It is important with Compazine and Trilafon particularly, and occasionally leads to rejection of the drug or avoidance of treatment. Restlessness which is so severe that it does not allow the patient to remain seated or lying in bed at appropriate times, in spite of the fact that fundamental psychotic mechanisms are at the same time relieved, is extremely unpleasant. The chief means for relieving this state of "turbulence" is modification of dosage; it can usually be avoided by starting with relatively small doses and increasing the dose gradually to a completely effective level. The management of somnolence is not usually a problem because it is usually a transient and mild effect with this group of drugs.

The symptom listed in Table 3 as "weakness" is related both to the state of consciousness and to the effect of the drug on neuromuscular ability. In some patients this seems to be sufficiently intense to require modification of dosage and careful increases with small increments. It is possible that some of the tabulated patients actually represent extrapyramidal and dystonic effects rather than direct neuromuscular effect. Such observations are difficult to evaluate in a purely clinical manner and will require careful physiologic studies over a long period to determine accurately their significance.

The central autonomic action of these substances is often expressed in trophic and endocrine changes in the patient.

TABLE 3.—EFFECT ON MOTIVATION AND AFFECT

	Thorazine	*Compazine*	*Trilafon*	*Vesprin*	*Winthrop #13,645–5*
Number of patients	1227	667	206	176	94
Excessive somnolence	26	19	4	2	6
Evidence of depression	—	17	0(?)	0	0
"Weakness"	27	26	6	3	2
"Turbulence" or "tension state"	—	19	6	0	0

Some of these are listed in Table 4. It is noteworthy that jaundice has not occurred in treatment with the four substances being discussed. The weight gain which has long been recognized as an important effect of chlorpromazine has not been seen with the lower dose compounds. It seems that in some instances the effect on psychoneurotic eating habits is favorable with Compazine and Trilafon. Our observations regarding sexual potency are not considered to be of sufficient accuracy to be reliable, but some mention of this where it has formed the basis for an actual complaint is made. Lactation has been observed by Ayd[1] in a much greater proportion of patients than by us in our series with chlorpromazine. We have seen lactation rarely with Compazine and Trilafon. Jaundice and

agranulocytosis have occurred only with chlorpromazine.

The neurologic effect of these drugs is closely related to actual therapeutic efficiency (Table 5). It is noteworthy that all of these substances can produce parkinsonism-like activity in practically any individual when the dose level is high enough for a sufficient period of time. The therapeutic effect on psychotic manifestations is in the majority of patients achieved without production of parkinsonism. It is, however, often necessary to push the administration of the drug to the development of such manifestations to achieve significant changes in psychotic manifestations and mechanisms. The parkinsonism-like syndrome is to be considered an index of therapeutic effect

TABLE 4.—"TROPHIC" AND ENDOCRINE EFFECTS

	Thorazine	*Compazine*	*Trilafon*	*Vesprin*	*Winthrop #13,645–5*
Number of patients	1227	667	206	176	94
Nausea	17	11	0	0	0
Constipation	4	2	1	0	0
Jaundice	5	0	0	0	0
Change in Libido	+	+	+	?	?
Lactation*	3	1	2	0	0
Agranulocytosis	4	0	0	0	0
Weight:					
No. of patients Recorded	847	640	207	180	110
Gained 10% or more	297	52	12	4	3
Lost 10% or more	37	44	3	6	2

*These figures may be low, but this effect was routinely checked and reported when positive.

TABLE 5.—NEUROLOGIC EFFECTS

	Compazine	*Trilafon*	*Vesprin*	*Winthrop #13,645–5*
Number of patients	667	206	176	94
"Dystonic" manifestations	11	2	0	2
Parkinsonism	251	47	30	31

TABLE 5a.—PARKINSONISM DETAIL

	Compazine mg./day		*Trilafon mg./day*	
	Less Than 76	*76 and Over*	*Less Than 25*	*25 and Over*
Before 1 month	44	4*	11	*
After 1 month	147	56	18	18
	Vesprin mg./day		*Winthrop #13,645–5 mg./day*	
	Less Than 76	*76 and Over*	*Less Than 76*	*76 and Over*
Before 1 month	3	1*	11	*
After 1 month	12	14	17	3

*Very few patients in this dose range before 1 month of treatment.

analogous to the slowing of the pulse and production of arrhythmias by digitalis in the management of cardiac conditions. Dystonic manifestations such as torticollis, spasm of the muscles involved in speech and deglutition and odd changes in gait and other motor manifestations, are closely allied to parkinsonism and are susceptible to the same methods of management. Parkinsonism produced by these drugs is always susceptible to the use of antiparkinson drugs, particularly Cogentin, Kemadrin and Pagitane. In our experience, Artane has not proved adequately effective. It is at times advisable to reduce the dose of drug and rarely, particularly with the dystonic manifestations, to withhold the drug for a sufficient period for the patient to recover from the parkinsonism or dystonia. Table 5a indicates the relationship of dosage and time to the development of parkinsonism. It is necessary, however, to point out that the higher doses in practically all of our patients are reached only after one month of administration of the drug and the tabulation is, therefore, significant only in the lower dose range, and a rough index in the higher dose range. In our experience, the lowest dose of drug with which parkinsonism has been produced is: Compazine 30 mg. per day, Trilafon 12 mg. per day, Vesprin 75 mg. per day, and Winthrop #13,645–5 37.5 mg. per day.

Results of Treatment. The effectiveness of these drugs in the treatment of chronic psychotic states is indicated in Table 6, the legend to which indicates a practical and useful grading scheme. The table has been condensed for the sake of brevity. Only the period of hospitalization prior to treatment is indicated, since duration of illness is usually difficult to establish in state hospital patients. The table includes only patients who have been treated 3 months or more with the indicated drug. It is apparent that 3 months is not sufficient time for achievement of adequate recovery at the "A and "B" level in many patients. Table 7 indicates the necessity for continued treatment to achieve a maximum level of benefit. Continued treatment, with every drug for which adequate experience is available, produces an increasing proportion of "A" and "B" results in any closed group of patients, as the time of treatment progresses from 3 to 6 to 9 and even to 12 months. This has previously been shown for chlorpromazine and reserpine and is now as clearly evident with Compazine, Trilafon and Vesprin. It is noteworthy that such continued treatment does not add to the hazard of drug therapy at all since the severe and serious toxic manifestations of drug effect occur preponderantly within the first 8 to 12 weeks of treatment. It is also noteworthy particularly from the state hospital point of view that the proportion of actual complete failures of drug therapy diminishes as time of treatment progresses.

The moderate improvements rated "C" that have made it possible to eliminate practically all of the restraint previously necessary in our hospital, and to eliminate completely the "deteriorated wards" where formerly denudative, incontinent patients resided, are still considered significant, even though they have not been tabulated. It is particularly the drugs which do not produce sedation such as Compazine, Trilafon and Vesprin which have made it possible for chronic, withdrawn schizophrenic patients to become approachable by properly motivated attendants and to be retrained in the civilized amenities which they had long since given up. It seems in the light of our newer experience that the sedation produced by chlorpromazine and reserpine served to make such ap-

TABLE 6.—GROSS RESULTS OF TREATMENT

Time in hospital (years)	*Compazine* 0–2	*Compazine* over 2	*Trilafon* 0–2	*Trilafon* over 2	*Vesprin* 0–2	*Vesprin* over 2	*Winthrop #13,645–5* 0–2	*Winthrop #13,645–5* over 2
Schizophrenia:								
No. of patients	119	201	30	42	21	41	7	12
"A" and "B" results	57	33	14	7	5	6	1	3
	47.8%	16.5%	47%	17%	24%	15%		
Affective psychoses:								
No. of patients	17	35	5	3	6	4		
"A" and "B" results	8	5	4	0	3	0		
	47%	14%						
Miscellaneous: (Chiefly chronic brain syndromes)								
No. of patients	90	82	11	11	14	14		
"A" and "B" results	22	9	3	0	1	2		
	24%	11%						

CRITERIA FOR IMPROVEMENT

"A": Patients who have recovered from all active psychotic manifestations, particularly have lost all delusions and hallucinations, have insight into previous delusions and hallucinations, have adequate affect, social and industrial adaptive capacity, equal at least to the premorbid level; and no overt hostility, particularly to the hospital or its staff.

"B": Individuals who have recovered from most psychotic manifestations, but may not have lost belief in previously present delusional experience, who are able to make a satisfactory social and industrial adaptation away from the hospital or in the hospital under privileged conditions, whose improvement may be summarized as "a good social remission."

"C": Patients who have improved from the initial condition in significant ways, particularly in ability to communicate verbally, in diminution or absence of assaultiveness, incontinence, denudativeness, and other gross manifestations of psychosis, and in some diminution of psychopathologic manifestations such as delusions and hallucinations without actual resolution of these.

"D": Patients who have improved only slightly or not at all.

TABLE 7.—EFFECT OF TIME ON RESULT

	Compazine	*Trilafon*	*Vesprin*
No. of patients in closed group	126	67	32
"A" and "B" Results			
At:			
3 mos.	13	9	10 (0 = "A")
6 mos.	35	24	10 (2 = "A")
9 mos.	39	—	—
"D" Results			
At:			
3 mos.	23	18	4
6 mos.	9	12	2
9 mos.	7	—	—

proach more difficult because these drugs "tranquilized" the patients only into less destructive activity without stimulating the relationships leading to the rehabilitation now achievable.

For those who have the "double-blind" compulsion, we have prepared Table 8. This indicates the effect of treatment of patients with Compazine after failure of treatment with chlorpromazine for 3 months or more (for most patients 6 months or more). The chlorpromazine is in effect what might be called "an active placebo." Only

patients who have not achieved or have relapsed from an "A" or "B" result as the result of treatment with chlorpromazine were used in this part of the study. Therefore, only the "A" and "B" results from Compazine following chlorpromazine failure are significant. It is evident that Compazine achieves significant beneficial effects on psychoses after chlorpromazine failure. Unfortunately for the members of the "double-blind" cult, I must introduce as a provocative "nonconditioned" stimulus the problem raised by the element of time which was just shown to be an important factor in producing recoveries when treatment with any one of these substances is continued over longer and longer periods.

TABLE 8.—COMPAZINE TREATMENT AFTER THORAZINE FAILURE OR RELAPSE, 178 PATIENTS TREATED AT LEAST 3 MONTHS WITH EACH DRUG

	Thorazine Result				*Compazine Result*			
Time in Hospital	*A**	*B**	*C*	*D*	*A*	*B*	*C*	*D*
0–6 months	4	6	2	1	2	9	2	
6 mos.–2 years	1	4	21	7	2	9	22	
2–5 years	1	3	24	8		9	25	2
5–10 years		2	21	8		4	25	2
Over 10 years		4	28	33		5	43	17

*"A" and "B" patients in this group had relapsed for various reasons, chiefly cessation of medication.

Discussion. Experience in treatment of psychotic patients with this group of compounds, which is characterized by a lower effective dosage range, has brought out certain important facts. Most important is the fact that in this large number of patients, there has not developed any severe toxic effect. There has been no jaundice and no agranulocytosis. It is, of course, necessary to have several thousand cases treated with each individual drug before the relative freedom from this form of blood dyscrasia can be determined. It seems at this point, however, that the incidence is definitely lower than with chlorpromazine, promazine and mepazine. It is also evident that the allergy-like manifestations are much less frequent in the useful dose range. We believe that our conservatism in the rate of increase of dosage has reduced the possibility of occurrence of severe toxic effects of these very potent drugs.

Trophic and endocrine effects of this entire group of compounds are in many respects similar to those of chlorpromazine, but at the dose levels which are useful in the treatment of psychoses, are likely to be milder than the effects of chlorpromazine. The absence of weight gain is in many patients gratifying.

The production of parkinsonism is considered a necessary physiologic index of drug effect and serves as an end point in the titration of drug against psychotic manifestations. This requires the same degree of attention and clinical skill that is required in the use of digitalis in the control of heart failure when the pulse rate approaches the low limits of usefulness and irregularities of cardiac rhythm occur.

The absence of somnolence and sedation in most patients treated with Trilafon, Compazine and Vesprin is a theoretically important as well as practically useful difference from chlorpromazine. It is evident that sedation is not a necessary accompaniment of pharmacologic benefit to psychotic symptoms such as delusions, hallucinations and the various manifestations of delirium. In a practical sense patients who are not made sleepy and sluggish are much easier to manage in hospital situations and are sooner ready for efforts at rehabilitation and the useful

varieties of psychotherapy. It is now more sharply evident that the principal effect of drug therapy in psychoses is the resolution of a disorder in control of the perceptive processes. Clearer understanding and appreciation of reality in its more complex aspects, particularly emotional and social, is gratifying to many patients and can be clearly described by those with adequate intelligence and language skill.

Differences between the drugs in the group under consideration are clearly evident clinically. Compazine and Trilafon are in many respects quite similar in their general clinical effect, except that Compazine tends to be somewhat more stimulating and Trilafon occasionally in its early use produces somnolence of minor degree that is quite rare with Compazine. Both produce "turbulence" at times, but this is more frequently of clinical importance with Compazine. Parkinsonism can be produced by smaller doses and apparently somewhat more quickly with Trilafon than with Compazine. The effectiveness on psychotic symptoms of this pair is at this time not clearly distinguishable.

Vesprin seems to be much milder in the production of side-effects than either Compazine or Trilafon. In our series, a lower level of parkinsonism is probably the reflection of a somewhat more conservative dosage scheme used with this drug than with the others. No turbulence has been observed with the use of Vesprin. It is probably somewhat easier to manage in dosage than any of the other compounds because of this mildness, but increase in dosage range is productive of more side-effects. To some extent, our figures indicate that we have been at fault in this, and have, therefore, had somewhat less brilliant results in the psychotic states with Vesprin. This in our group of patients, however, may be the reflection of nonrandom choice of patients which can influence results more than any other one factor.

Winthrop #13,645–5 is an extremely effective drug with intense pharmacologic effects on psychotic manifestations. There is marked tendency to produce sedation of psychotic manifestations without actual influence on the level of consciousness. This is the only drug which has produced hypotension similar to that produced by chlorpromazine. It is, however, definitely less frequent than with chlorpromazine. A clinical curiosity that is to be mentioned is the patient who had had a sympathectomy for hypertension and developed hypotension from Winthrop #13,645–5 in two separate periods and was unable to tolerate the medication.

Under state hospital conditions, it becomes apparent that the management of large groups of patients on drug therapy is facilitated by the use of lower dose compounds since fewer side-effects and practically no toxic effects are produced. Close attention to clinical detail must be maintained and the susceptibility of patients to beneficial attention from attendants, nurses and physicians must be exploited fully to produce the maximum proportion of improved and recovered patients. These principles have in our hospital produced dramatic and gratifying advances even from the progress which had been effected from the large-scale application of chlorpromazine.

Finally, I would like to point out what seems to me to be an historical analogy. At the time of introduction of the sulfonamides in clinical medicine in the middle 1930's, sulfanilamide was the most important compound. Subsequently, many derivatives of closely related chemical structure were found

to be more useful and considerably safer and more acceptable. Indeed, more than 20 years later, we are still seeking and putting into use new sulfonamide drugs. It seems that chlorpromazine is in this situation the analogue of sulfanilamide and the newer psychopharmacologic drugs chemically related are analogous to the newer, more effective, and safer sulfonamides. It is to be hoped that we may even be able to develop certain kinds of specificity of neuropharmacologic and psychopharmacologic effects of clinical usefulness as our knowledge of the illnesses which we are treating improves, particularly from the impetus given to the knowledge by the use of these drugs.

Summary. Four phenothiazine compounds, related to chlorpromazine were investigated for effectiveness in treatment of psychotic states in significant numbers of patients: Compazine (prochlorperazine), 667 patients; Trilafon, 206 patients; Vesprin 176 patients, and Winthrop #13,645–5, 94 patients. All of the patients were confined in a state mental hospital and were suffering from chronic psychoses. The chief differences between these compounds and the previously familiar phenothiazine derivatives such as chlorpromazine, promazine and mepazine are 1) more intense pharmacologic and therapeutic activity and consequent smaller dosage level; 2) much less frequent occurrence of side-effects and toxic complications from use of the drug. Particularly important is the absence of jaundice after the use of these compounds, and in the series thus far observed, absence of agranulocytosis. These drugs are also characterized by production of little or no sedation, in contrast with chlorpromazine and reserpine, but have much greater beneficial effect on psychotic manifestations such as delusions and hallucinations and pathologic excitement. The side-effects are tabulated as 1) allergy-like manifestations, 2) "trophic" and endocrine effects, and 3) neurologic effects. Management and significance of these is considered in detail. The chief neurologic effect, parkinsonism, is often (but not always) to some degree a necessary accompaniment of therapeutic benefit in treatment of psychoses, and should be managed by manipulation of dosage and use of Cogentin in addition to the active drug. These drugs are particularly effective in treatment of schizophrenia, manic-depressive psychoses in the manic group, and synergistically with electro-shock in the depressed group; and organic delirium. They represent a distinct advance in pharmacologic treatment of psychoses.

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(Interlingua on page 99)

SUMMARIO IN INTERLINGUA

(See page 60 for original article)

Diffuse Fibrose Pulmonari Interstitial (Syndrome De Hamman-Rich) In Un Patiente Allergic: Reporto De Un Caso

Nos presenta un caso de diffuse fibrose pulmonari interstitial (cognoscite como syndrome de Hamman-Rich). Le diagnose esseva confirmate per biopsia pulmonar. Le patiente habeva un historia personal e familial de allergia. Therapia a prednisona, continuate durante un periodo de 20 menses, resultava in marcate grados de alleviamento symptomatic con coincidente melioration del saturation de oxygeno arterial e leve, ben que definite, signos de melioration in le configuration roentgenographic. Le possibilitate que iste morbo representa un reaction allergic a un droga esseva considerate sed non poteva esser demonstrate in le presente caso. Tamen, le patiente ha un historia de continue inhalation de vapores irritante durante un periodo de al minus 2 annos ante le declaration de su symptomas. Iste debe esser considerate como un possibile factor etiologic in un patiente de si alte grados de susceptibilitate.

SUMMARIO IN INTERLINGUA

(See page 50 for original article)

Therapia Experimental A Hormones In Le Tractamento De Atherosclerosis: Observationes Preliminari Super Le Effectos De Duo Nove Compositos

Es reportate observationes preliminari in re le effectos de duo nove compositos in patientes con atheroscleosis coronari. Illos es comparate con le action de substantias estrogenic conventional. Le premissa que le modo de distribution de lipoproteina seral que es typic de juvene femininas representa un standard desirabile esseva acceptate tentativemente, e effortios de effectuar ille modo sin excessos de femininisation esseva facite. Iste effortios succedeva in 65% del patientes tractate con Manvena (que es un del duo compositos in question), sed paradoxemente 15% monstrava un effecto contrari. Altere signos de melioration objective non esseva definitemente establite, ben que un certe suggestion de melioration electrocardiographic e ballistocardiographic, specialmente ballistocardiographic, in comparation con le expectationes justificate in patientes non tractate poteva esser notate. Super le base de iste relativemente breve observationes il pare que le possibilitate existe de instituer un prolongate therapia a Manvena in quantitates sufficiente pro influentiar favorabilemente le stato del lipidos seral (e possibilemente altere mesurationes objective) e de obtener intolerabile grados de femininisation in multo plus basse numeros de patientes que es le regula in ordinari tractamentos estrogenic. Es necessari sublinear emphaticamente que iste forma de tractamento es experimental. Illos non debe esser applicate sin discrimination in le tractamento de patientes con atherosclerosis coronari usque plus definitive provas human ha devenite disponibile.

PROGRESS
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UNDER THE CHARGE OF

GEORGE E. BURCH, M.D.
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA
NEW ORLEANS, LOUISIANA

AND

C. THORPE RAY, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA
NEW ORLEANS, LOUISIANA

HYPOTHALAMUS AND THE ENDOCRINE CONTROL OF SODIUM AND WATER METABOLISM IN MAN*

BY JOSEPH F. DINGMAN, M.D.
ASSISTANT PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA
NEW ORLEANS, LOUISIANA

(From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans, New Orleans, Louisiana)

DISTURBANCES in sodium and water metabolism represent some of the commonest therapeutic problems in clinical medicine today. Renal retention of sodium and water has become widely recognized as an almost universal accompaniment of disease, and evidence is growing that this retention is mediated through the central nervous system to the hypothalamus and thence to the endocrine glands, which regulate renal excretion of sodium and water. It would seem desirable at this time to summarize current knowledge of the influence of the hypothalamus and certain endocrine organs on sodium and water metabolism in health and disease in order to derive tentative conclusions upon which therapeutic measures may be based.

The following aspects of the subject will be discussed:

1. Neurohypophysis and water metabolism.
   a. General considerations.
   b. Mechanisms of secretion of antidiuretic hormone (ADH).
   c. Factors influencing ADH release.
   d. Measurement of ADH in body fluids of man.

*The original research reported in this article has been supported, in part, by grants from the National Heart Institute (H 2106 and H 2850), National Institutes of Health, and the Louisiana Heart Association Inc.

2. Adrenal cortex and sodium metabolism.
   a. General considerations.
   b. Relation of adrenal cortical secretion to sodium excretion.
   c. Aldosterone.
3. Adrenal cortical–neurohypophyseal relations.
4. Role of the hypothalamus.
5. Therapeutic implications.

Although the states of the circulation and of the kidney are of fundamental importance for filtration and excretion of sodium and water, these factors will be discussed here only in regard to their interrelations with the endocrine system. For more detailed information, the reader is referred to recent comprehensive reviews on the subject[12,52].

Neurohypophysis and Water Metabolism. GENERAL CONSIDERATIONS. The antidiuretic hormone of the neurohypophysis (ADH, vasopressin) is generally recognized as the principal agent that regulates water excretion in mammals[117]. Its primary action is to enhance reabsorption of solute-free water by the distal tubule of the kidney[128].* The importance of the posterior lobe of the pituitary body in water conservation has been known for a little more than four decades, after independent reports were published in 1913 by Farini[39] and von den Velden[113] of the antidiuretic action of posterior pituitary extracts. Kamm and associates[62] fractionated posterior lobe extracts into two main components, referred to as Pitressin (vasopressin) and Pitocin (oxytocin). Highly purified hormonal fractions were subsequently obtained from posterior lobe extracts by Potts and Gallagher[91,92], Stehle and Fraser[108] and van Dyke and associates[35]. However, the systematic efforts of du Vigneaud[119] and his colleagues in the last decade have led to purification of naturally occurring vasopressin[121] and oxytocin[87] and, more recently, to successful synthesis of both hormones[120, 122]. Both hormones are polypeptides containing 8 amino acids per molecule, 6 of which are identical in each and 2 are different.

Although these hormones are separate polypeptides with distinct biologic properties, the problem remains as to whether they are secreted from the neurohypophysis in this form or represent active fragments of a single large protein molecule possessing both activities in equal proportion[35]. Recent studies of the hormonal content of plasma proteins have demonstrated significant gonadotrophic[5], corticotrophic[11], and possibly antidiuretic[26] activities in macromolecular fractions; this may be interpreted as evidence for secretion of relatively large proteins from the pituitary gland. On the other hand, small polypeptides of pituitary origin may be released as such into the circulation and subsequently become bound to the plasma proteins for transport purposes only.

MECHANISMS OF SECRETION OF ANTIDIURETIC HORMONE (ADH). Demonstration of active hormonal principles in the posterior portion of the pituitary body led to extensive investigation of the endocrine function of this lobe. For some time, glial cells in the posterior lobe, which were called "pituicytes"[14], were thought to represent hormone-producing cells. Fisher, Ingram, and Ranson[41] showed that lesions that destroyed the supra-optic-hypophyseal tract led to degeneration of the neu-

*The urinary volume may be divided into two moieties known as osmolar water and solute-free water. Osmolar water is that portion required to contain the urinary solutes in a solution isosmotic to plasma; the remaining urinary volume is composed of solute-free water. These indices have been designated osmolar clearance (C_{OSM}) and solute-free water clearance (C_{H_2O}) by Wesson and Anslow[124]. Solute-free water is abstracted from the urine during ADH action and is contributed to the urine during water diuresis, when ADH activity is depressed.

rones of the supra-optic and paraventricular nuclei, atrophy of the posterior lobe, and development of diabetes insipidus. This study emphasized the importance of hypothalamic neurones in endocrine secretion, but the hypothesis that these cells merely exerted a neurotrophic influence on secretory cells of the posterior lobe seemed plausible and conclusive at that time. However, even before this study was begun, Scharrer and Scharrer[103] were investigating neurosecretory activity in the central nervous system of vertebrates and, in 1949, a member of their laboratory, Bargmann[6] demonstrated neurosecretory granules within the neurones of the supra-optic and paraventricular nuclei, using Gomori's stain for the beta cells of the pancreatic islets. The efforts of these workers and others[56] have led to a concept that has become widely accepted in recent years, that is, that the hormones of the posterior lobe of the pituitary gland are secreted by the neurones of these hypothalamic nuclei, transported distally along the axones, and stored in the posterior lobe within nerve endings in close proximity to blood vessels of this region. The posterior lobe, therefore, may serve merely as a reservoir of preformed hormone readily available for release into the systemic circulation to meet the immediate needs of the organism. These studies represent a fundamental advance in endocrinology in directing attention from the pituitary body to the hypothalamus as the structure governing water metabolism.

FACTORS INFLUENCING ADH RELEASE. The role of the antidiuretic hormone in water metabolism was clearly established by Verney[116], who ascribed the regulation of water excretion to an osmoreceptor located within the distribution of the internal carotid artery. This osmoreceptor is sensitive to changes in osmotic pressure of the plasma and modifies the rate of ADH release from the neurohypophysis in accordance with the state of hydration. Its exact location is unknown, but description of vesicles within the neurones of the supra-optic nuclei have been interpreted as intracellular osmoreceptors[61]. The fact that Andersson and McCann[4] produced polydipsia and inhibition of water diuresis by injecting a hypertonic solution of saline into the anterior portion of the hypothalamus of goats would lend credence to Verney's hypothesis as to the site of the osmoreceptor. However, the effect of this injection was not reproducible[3] and could have been due to nonspecific stimulation of the hypothalamus rather than directly to the hypertonic solution.

One patient with diabetes insipidus secondary to metastatic carcinoma of the posterior lobe of the pituitary body failed to respond to infusion of a hypertonic saline solution but had a normal antidiuretic response to nicotine; such a reaction suggested preservation of some neurohypophyseal function that was not responsive to hypertonicity[23]. Postmortem studies of the neurohypophysis with Gomori's stain demonstrated numerous secretory granules within the neurones of the intact supra-optic nuclei, but the infundibular stalk and posterior lobe were extensively infiltrated by malignant cells and were devoid of neurosecretory material. These studies suggested that the osmoreceptor may be outside the supra-optic nuclei, possibly in the posterior lobe, since osmoreceptor control of available ADH was apparently lost.

Additional evidence that the osmoreceptor response may be destroyed by removal of the posterior lobe has been obtained from studies of the mechanisms of ADH secretion in patients hypophysectomized for metastatic carcinoma of the breast[29]. After removal of the posterior lobe, the

osmoreceptor response to hypertonic saline infusion was absent more frequently than was the response to nicotine. Thus, osmoreceptor activity may depend on preservation of a portion of the posterior lobe or the stalk, and release of ADH from the hypothalamus may be influenced by nicotine and other central stimuli but not by changes in osmolarity of plasma. Determination of the pathways of communication between the osmotic pressure of the blood and the neurohypophysis is more than an academic question, since osmotic control of ADH release is intimately related to the retention of water and formation of edema.

ADH release may be produced by various emotional, physical, and physiologic stimuli as well as by numerous drugs, including ether, barbiturates, morphine, acetylcholine, and nicotine[32,87]. Small doses of adrenalin inhibit, and large doses stimulate, ADH release in animals[117] but not necessarily in man[15]. Recent studies have shown that adrenal cortical hormones may influence ADH release in man[30] as well as in experimental animals[44].

A poorly understood pathway to the neurohypophysis is that involving alterations in volume of the vascular system. A "volume receptor" promoting sodium and water retention has been located in the cephalic portion of the vascular tree[73]; it may be activated by many factors that decrease circulating or "effective" blood volume[52]. The reports of prompt secretion of large amounts of ADH in response to hemorrhage[47,48] would support a role of the neurohypophysis in regulating volume. The activity of the volume receptor can be blocked by simultaneous obstruction of venous drainage from the head[73,118]. Retention of water by such maneuvers may be inhibited in some instances by prior administration of alcohol[84], which may involve the neurohypophysis in the antidiuretic response. The fact that retention of sodium is not blocked by alcohol[84], suggests that this retention may not be mediated directly through vasopressin secretion. However, oxytocin is also released in large amounts with neurohypophyseal stimulation[54] and has been shown to have definite effects on sodium excretion in appropriate circumstances[13], although, in itself, it is only slightly antidiuretic[33].

In view of these observations, intensive investigation of the quality of neurohypophyseal hormones released in response to various endogenous and pharmacologic stimuli seems clearly indicated and may ultimately implicate the neurohypophysis in sodium retention. Ability to alter the ratio of vasopressin to oxytocin in the neurohypophyseal outflow may provide independent means whereby the hypothalamus may regulate excretion of sodium and water according to the needs of the organism[13].

Various hypotensive drugs produce considerable retention of water largely as a result of their effect on renal circulation or innervation[45,82,83]. Since these drugs have potent effects on the midbrain, they may, possibly, also facilitate retention of water by stimulating ADH release. Such an effect on neurohypophyseal secretion has recently been reported for hexamethonium[123].

Thus, many apparently unrelated factors influence release of neurohypophyseal hormones into the systemic circulation. Some of these stimuli may reach the neurohypophysis primarily by afferent nervous pathways to the hypothalamus. Others may alter the vascular supply of hypothalamic nuclei and the posterior lobe, and variations in concentration of water or total solute of blood supplying this region may influence the neurohypophysis by yet another receptor system. The divergent

nature of these stimuli may explain the peculiar anatomic and secretory organization of this gland, in which hormones made by the central nervous system are transported relatively great distances and stored in the highly vascularized posterior lobe, which possesses an independent circulation. Each stimulus, therefore, may use a separate pathway to the neurohypophysis, nervous impulses affecting the nuclei directly, volume factors influencing both hypothalamic and posterior pituitary circulation, and osmoregulation possibly confined to the posterior lobe. This arrangement would permit the hypothalamus, in a sense, to monitor each stimulus and allow those of greater intensity or biologic need to dominate neurohypophyseal activity.

The three major modalities that promote ADH release, in ascending order of priority, are osmoregulation, volume regulation, and neurogenic stimulation, and probably all three can act in combination. On the other hand, inhibitory impulses are probably effective only when pathways of stimulation are quiescent. I must assume full responsibility for this arbitrary classification, yet some information lends a semblance of reason to this scheme. For instance, volume contraction or neurogenic stimuli evoke ADH release in the presence of hypotonicity, and nervous impulses take precedence over the inhibitory effect of expanded volume. Except for hypnosis[77], neurogenic inhibitors are relatively unknown. However, patients with psychogenic polydipsia may possibly have a derangement in neural control of the neurohypophysis[23]. Hypertonic contraction of blood volume produces more potent antidiuresis than does hypertonicity alone, yet hypertonic expansion of blood volume, if acutely induced, will evoke ADH discharge. This implies precedence of stimulating osmotic impulses over inhibitory volume impulses. This priority system seems reasonable if the primary functions of the neurohypophysis in fluid metabolism are, first, to preserve tonicity but, fundamentally, to protect the volume of body water. Neural regulation is deemed of paramount importance in view of the need for conservation of body resources during severe stress by decreasing the loss of extracellular fluid in the urine, regardless of its volume or composition, as well as by providing increased amounts of neurohypophyseal hormones as needed for proper muscular activity[59].

MEASUREMENT OF ADH IN BODY FLUIDS OF MAN. Current studies of neurohypophyseal function in man are handicapped by serious gaps in our knowledge of the ADH content of body fluids in health and disease. Numerous investigators have reportedly demonstrated abnormal amounts of ADH in plasma and urine of man and experimental animals in various situations. Van Dyke and co-workers[33], in a recent review of this subject, advanced sound reasons for viewing most of these studies with reservation; many methods of assay have been nonspecific, and response of animals to different routes of administration of assay material has varied.

Recently, interest in the diuretic effects of alcohol has been rekindled[36]. The fact that alcohol depresses ADH secretion[1] has suggested its use in biologic assay of ADH[2,21,37], which generally involves intravenous injection of assay material into alcohol-anesthetized normal rats. Although this preparation is exquisitely sensitive to Pitressin (as little as 20 micro-units) the propriety of its use for assay of antidiuretic activity in plasma or urine is somewhat questionable, since alcohol probably does not inhibit activity of the posterior lobe sufficiently to pre-

vent ADH release in normal animals in response to potent neurohypophyseal stimuli or to substances other than ADH in the assay material. This conclusion is based on the observation of increased secretion of ADH in response to hemorrhage[47,48] or etherization[2] in rats under alcohol anesthesia. Studies in normal man have shown that administration of ethanol elevates the threshold dose of nicotine required to stimulate ADH release but does not block the antidiuretic response to slightly larger doses of nicotine[22].

Proper determination of ADH in biologic fluids of man requires not only a suitable assay preparation devoid of neurohypophyseal function to prevent false positive results but also reliable techniques for concentration of the minute amounts of ADH believed to be present in normal plasma or urine. Various methods for biologic assay of ADH in serum or urine have been under investigation in my laboratory for some time. Attempts to assay whole urine and plasma by intravenous injection into hydrated normal dogs according to the technique of van Dyke and associates[34] frequently resulted in nonspecific, stress-induced antidiuresis undoubtedly as a result of discharge from the posterior lobe rather than of injected ADH. Efforts to procure reliable assay animals led to the use of dogs with diabetes insipidus induced by electrocoagulation of the median eminence of the hypothalamus kindly prepared by Dr. David Hume. All dogs had clearcut antidiuretic responses to neurohypophyseal stimulation postoperatively. Administration of large doses of adrenal steroids, however, subsequently rendered one animal unresponsive to neurohypophyseal stimuli; this dog was used for assay of antidiuretic activity of plasma and urine of man until its death from anaphylactic shock[26].

During the course of these experiments, various protein fractions of pooled normal plasma, prepared according to the method of Cohn and co-workers[17], were studied, and only one of these (Fr. II + III) had any antidiuretic activity (Table 1). Although the response appeared to be typical of the action of ADH on excretion of solute-free water, these results must be viewed guardedly until a larger series of suitably prepared animals is studied. Demonstration of antidiuretic activity of this magnitude in plasma (approximately 5 micro-units Pitressin per ml. whole plasma) is within predicted normal concentrations of plasma ADH of man proposed by Lauson[69] and van Dyke and associates[33], which should encourage further investigation of this technique of study.

Adrenal Cortex and Sodium Metabolism. GENERAL CONSIDERATIONS. The adrenal cortex is the major endocrine gland that regulates the sodium content of the body. The principal adrenal cortical steroid hormones known to influence electrolyte metabolism in man are hydrocortisone (Compound F), corticosterone (Compound B), and aldosterone. Compounds F and B, which represent the major secretory products of the human adrenal gland have been estimated by Sweat[110] to be secreted in the ratio of approximately 4:1, but Peterson[86] has recently reported plasma ratios of 13:1 in normal man. The human adrenal gland has been estimated to secrete from 17 to 29 mg. Compound F[86a] and 2 to 3 mg. Compound B[86] daily. The adrenal content of aldosterone, however, is extremely small (45 to 95 μg. per kg. beef adrenal gland)[125], and only traces are found in normal venous blood[104] or urine[7,71]. Although the present intense interest in the mechanisms of secretion of aldosterone has overshadowed the importance of other known adrenal

steroids in regulation of electrolyte excretion, they possess definite physiologic effects that must not be discounted if the role of the adrenal cortex in sodium metabolism is to be clarified.

RELATION OF ADRENAL CORTICAL SECRETION TO SODIUM EXCRETION. Secretion of hydrocortisone[64,79] and corticosterone[85] in normal man has a diurnal rhythm which is highest in the early morning, falls sharply in the late afternoon, and reaches its lowest level during sleep. Although a similar diurnal rhythm in excretion of aldosterone has been suggested[114a], a consistent trend was not observed, since in 8 of 19 determinations, essentially no difference was observed between day and night values, or greater excretion occurred at night. A diurnal pattern for sodium excretion, which is predominantly determined by alterations in renal tubular reabsorption of this element[106], lags behind the adrenal rhythm by only a few hours, its peak occurring in the forenoon or at midday. The association of these patterns may be more than accidental and implies a possible physiologic interrelation between adrenal secretion and sodium excretion.

TABLE 1.—EFFECT OF HUMAN PLASMA PROTEIN FRACTIONS ON EXCRETION OF WATER

Dog: 15 kg. ♀
Diabetes insipidus
50 mg. cortisone I.M./day

Procedure	*Urinary volume (ml./min.)*	C_{H_2O} *(ml./min.)*	*Cosm (ml./min.)*	*Urine (mOsm./L.)*	*Duration antidiuresis (min.)*
20 ml./kg. constant water load	1.40*	+0.44	0.96	202	
0.1 m.u.¶ Pitressin I.V.	0.86	+0.10	0.76	262	30
26 ml. albumin fraction† (200 ml. plasma)‡	3.05	+2.12	0.93	90	
20 ml. Fr. IV-1 (200 ml. plasma)	2.65	+1.83	0.82	91	
20 ml. Fr. IV-4 (200 ml. plasma)	5.00	+3.84	1.16	69	
7 ml. Fr. II + III (50 ml. plasma)	1.10	+0.76	0.54	124	40
21 ml. Fr. II + III (150 ml. plasma)	0.73§	−0.19	0.92	372	90
15 ml. fresh human plasma	3.30	+2.59	0.71	64	
0.5 m.u. Pitressin IV	0.30	−0.03	1.23	303	60
0.75 m.u. Pitressin IV	0.33	−0.24	1.24	365	>50

*Maximum diuresis.
†All fractions given I.V.
‡Values in parentheses refer to equivalent volumes of whole plasma.
§Urinary flow ceased for 40 minutes after injection.
Minimum urinary volume recorded = 0.35 ml./min.
¶m.u. = milli-unit.

Some current studies pertaining to this problem may shed light on the mechanisms involved. Compound F and its relative, cortisone, are not potent sodium retaining steroids and may result in loss of sodium when given in relatively small doses[60,110]. Recent reinvestigation of this phenomenon with intravenously administered steroids has demonstrated clearcut sodium diuresis in normal and Addisonian subjects who

had received physiologic doses of Compound F and a related compound, prednisone, retention of sodium being associated only with administration of large doses[27]. In both groups of patients, the predominant immediate effect of these hormones was to decrease renal tubular re-absorption of sodium. Administration of intravenous Compound F in doses of 1 mg. per hour to a patient with Addison's disease over a period of 24 hours elevated renal excretion of sodium during the day and blocked the sodium-retaining effect of a small dose of desoxycorticosterone acetate (DCA) given at 8:00 p.m.

These studies with physiologic doses of gluco-corticoids, if corroborated, suggest that the diurnal variation of excretion of sodium in normal subjects may be closely related to a rhythmic secretion of hydrocortisone, which influences renal tubular reabsorption of sodium. The nocturnal decline in excretion of sodium may be related not only to a decrease in secretion of Compound F but also possibly to unopposed effects of potent sodium-retaining steroids secreted at night.

Variations in extracellular fluid (ECF) volume have been shown to influence tubular reabsorption of sodium[109], but the mechanism of this action is unknown. Although the activity of volume regulators may be independent of the adrenal cortex to some degree[98], the state of the circulation and that of the adrenal cortex are undoubtedly intimately related. Adrenal steroids frequently produce expansion of ECF volume at the expense of intracellular volume[20,57,131] and may promote sodium diuresis by altering volume receptor activity[109]. Conversely, contraction of ECF volume has been shown to lead to sodium retention[52].

Conceivably, a diurnal rhythm in extracellular fluid volume parallels secretion of Compound F by the adrenal gland, leading to sodium diuresis during the day and retention at night. Until methods for estimation of small changes in ECF volume are perfected, however, the possible interrelations of ECF volume, adrenal cortical rhythms, and excretion of sodium can remain no more than an interesting speculation. Renal tubular effects of steroids may well prove to be more important in controlling excretion of sodium than are their volume regulating effects.

The initial sodium diuresis we have observed in normal subjects who had received small doses of Compound F or prednisone was frequently accompanied by a solute-free water diuresis, which was blocked by administration of Pitressin or nicotine[27]. A sudden decrease in antidiuretic influences on the renal tubules may possibly account for the transient sodium diuresis as well as the anticipated water diuresis. The influence of hydrocortisone-like steroids on ADH release, therefore, may promote sodium diuresis indirectly by altering neurohypophyseal activity. If adrenal steroids influenced only ADH release but did not alter discharge of oxytocin, a disturbance in the ratio of these polypeptide hormones, which act on the kidney, could also account for acute changes in excretion of sodium and water[13].

Compound B produces not only significant effects on organic metabolism but also is a fairly potent salt-retaining steroid[112] and has been used successfully to maintain Addisonian patients in satisfactory metabolic balance[18]. Although studies with this compound have been somewhat restricted by its limited supply, evidence of its effects is sufficient to warrant more detailed investigation of its role in sodium metabolism of normal man. Perhaps adrenal secretion of Compound B and

related steroids is sufficient to maintain salt balance in normal situations. Thus, production of more potent sodium-retaining steroids, such as aldosterone, may be required only when maximal retention of sodium is necessary to ward off sodium deficit or preserve extracellular osmotic pressure, for example, deprivation of salt, accumulation of fluid, and contraction of ECF volume.

ALDOSTERONE. The current status of aldosterone has been recently reviewed in detail[7,46]. This steroid, a close relative of Compound B, appears to possess much more potent sodium-retaining effects (20 to 30 times DCA) and some, but not all, gluco-corticoid actions. Its presence in traces in normal man has not clearly established a significant role for this hormone in electrolyte metabolism. However, the presence of increased amounts of this steroid in association with edematous states has led to intensive investigation of its role in the formation of edema.

Secretion of aldosterone is enhanced by deprivation[72] or depletion[8,9] of sodium and by administration of potassium[67] and is inversely related to ECF volume[7]. Factors related to body fluid volume may possibly have primary importance in regulation of such secretion. Studies of the relation of the anterior lobe of the pituitary gland to secretion of aldosterone have led to some controversy, as yet unresolved. Secretion of aldosterone has been shown to continue despite anterior pituitary insufficiency[71,114] and to increase when salt is restricted in these patients[74]. On the other hand, ACTH increases secretion of aldosterone to some degree in normal man[74] and in the isolated perfused beef adrenal gland[100].

In recent years, Farrell and coworkers[40,96] have demonstrated a diencephalic factor which regulates this secretion and have shown that some highly purified corticotropins enhance it, whereas commercial ACTH preparations do not. In addition, purified human and monkey growth hormone[94] have been shown by Beck and associates[10] to increase secretion of aldosterone in man. These observations suggest that separate trophic hormones of pituitary or hypothalamic origin may regulate production of this substance but that its continued secretion may be maintained in the absence of the pituitary gland by local factors, such as the volume or ionic composition of ECF or, more specifically, of the blood perfusing the adrenal gland. Large amounts of aldosterone are present in the urine of patients with cardiac[105], nephrotic[72], or cirrhotic[16] edema and with eclampsia[115]. However, the normal values in some edematous subjects[72] and the suppression of production of the hormone by administration of salt to others[31,50] would suggest that caution must be exercised against heavy reliance on these results to explain the pathogenesis of edema. Clarification of the role of the endocrine system in retention of sodium must await further knowledge of the pathophysiologic chain of events initiated by inadequacy of the circulation and ending in severe edema.

Adrenal Cortical-Neurohypophyseal Relations. Adrenal cortical hormones have been known for many years to facilitate water diuresis and protect against water intoxication. This effect is due primarily to an inhibitory action of adrenal steroids on distal renal tubular reabsorption of water[43]. On the basis of existing evidence, Gaunt and co-workers[43] championed the view that adrenal steroids antagonized the action of antidiuretic hormone on the renal tubule. Subsequently, Winter[127] suggested that cortisone may suppress ADH release in adrenalectomized rats.

By modern techniques of measuring renal excretion of solute-free water, cortisone was shown to increase such excretion during constant water-loading studies in normal subjects and patients with neurohypophyseal insufficiency[30]. Since the increased diuresis was associated with a decrease in osmolarity of the urine and inhibition of the antidiuretic response to nicotine but not to Pitressin, it was postulated that the diuretic effect of hydrocortisone-like steroids may be mediated through inhibition of ADH secretion from the neurohypophysis.

Further studies in normal subjects suggested that this inhibition appeared to be selectively on the hypothalamic (neural) control of ADH release, since these hormones did not alter the osmoreceptor control of ADH secretion[24]. Thus, it was concluded that water diuresis may not be analogous to a state of physiologic diabetes insipidus in all instances. According to this view, persistent secretion of ADH through a hypothalamic mechanism not regulated by extracellular tonicity governed the rate of water excretion during studies of water diuresis in normal or Addisonian subjects, and this antidiuretic mechanism could be suppressed by hydrocortisone-like adrenal steroids[25].

Gaunt, Lloyd, and Chart[44], who investigated these hypotheses by measuring the effect of adrenal steroids on ADH content of the hypothalamus or posterior lobe of hypophysectomized or adrenalectomized rats, concluded that corticoids either facilitate the synthesis or, more plausibly, inhibit the release of ADH. Recently, Raicz and associates[95] confirmed the action of hydrocortisone on excretion of solute-free water in man but concluded that this water diuresis represented a direct effect of steroids on renal tubular permeability to water independent of ADH. However, since their studies were performed in subjects on low sodium diets excreting maximally hypotonic urine during water diuresis, changes in ADH activity, reflected in a decline in urinary osmolarity below pre-existing levels, may not have been demonstrable.

Another interesting feature of the action of adrenal steroids on the neurohypophysis is the observation that potent salt-retaining steroids, such as 9 alpha-fluorohydrocortisone and desoxycorticosterone acetate, may occasionally increase sensitivity of the ADH release mechanism[24,44]. This phenomenon, if further substantiated, would suggest a dual mechanism for regulation of the rate of release of ADH and, therefore, of water excretion under the control of the adrenal cortex, which may be of fundamental pathophysiologic importance in the formation of edema.

Although small doses of glucocorticoids appear to exert definite natruretic effects, larger doses ordinarily used therapeutically regularly lead to sodium retention, reflecting a mineralo-corticoid action of all adrenal steroids when given in large amounts. The fact that gluco-corticoids may suppress ADH secretion would imply that adrenal steroids may result in sodium retention out of proportion to water retention. Water retention of some degree, however, is associated with cortisone therapy[107], and, occasionally, severe edema and even congestive heart failure may be observed. Curiously, significant retention of water has not been reported in association with aldosterone-secreting adrenal tumors[19] or, in some instances, with administration of aldosterone[51,93]. In the previously cited experiments with intravenously administered adrenal steroids, retention of water for the 24-hour period of hormone treatment was always much less than the theoretic volume required for

isosmotic equilibration of retained sodium[27]. Some of the adrenal steroids produced an initial solute-free water diuresis, possibly related to an immediate inhibitory effect of steroids on ADH secretion, and such water loss could theoretically result in relative hypertonicity of the body fluids and desiccation of the cells, if unchecked.

If adrenal steroids do not alter the osmoreceptor control of ADH[24], ADH release may be restored through osmoreceptor activation, and ADH secretion thereafter may be governed for the most part by the increment in extracellular sodium produced by the adrenal steroids. However, the potassium diuresis that regularly accompanies steroid therapy may offset the osmotic effect of retained sodium. This exchange of potassium for sodium would tend to minimize retention of total solute, and a shift of sodium into cells to replace the loss of intracellular potassium[38] may lessen the increment in extracellular sodium and decrease the water requirement for maintenance of extracellular osmotic pressure. The occurrence of edema with steroid therapy, therefore, should require augmented secretion of ADH or potentiation of its antidiuretic action for osmotic retention of sodium and water to occur. That this may be the case is suggested by a study[27] in which the quantity of sodium and water retained with combined administration of hydrocortisone and Pitressin intravenously more closely approximated the composition of extracellular fluid than when Compound F was administered alone; greater retention of sodium coincided with the additional retention of water.

If these observations are corroborated, they imply that persistent secretion of ADH may be necessary for isosmotic retention of sodium and water to occur during stress. The pattern of adrenal secretion during stress may be important in determining not only the degree of sodium retention but also the magnitude of water retention. An outpouring of salt-retaining steroids as well as gluco-corticoids in response to increased hypothalamic activity may provide endogenous checkmates for the suppressive action of hydrocortisone on the neurohypophysis and permit isosmotic retention of extracellular fluid.

Role of the Hypothalamus. Significant advances have been made in understanding the neural control of adrenal cortical secretion, and in recent years Harris[54], Hume[58], and others[78,90] have shown that the hypothalamus regulates secretion of corticotropin by releasing neurohormones into the hypophyseal portal vessels coursing downward from the region of the hypothalamus to the anterior lobe of the pituitary gland. Recent recognition of the pioneer studies of Scharrer and Scharrer[103] elevated the hormones of the posterior lobe to the level of hypothalamic neurohormones.

At the present time there is intense interest in the possibility that neurohypophyseal polypeptides closely resembling vasopressin may be responsible for the release of ACTH from the anterior lobe of the pituitary gland[53, 102], and even though this substance has not been identified, these studies indicate that this area of the hypothalamus may control not only ADH secretion but also secretion of electrolyte-regulating adrenal cortical steroids. The possibility that hormones of hypothalamic or anterior pituitary origin may govern secretion of aldosterone would further suggest a possible role of the hypothalamus in sodium metabolism, and the possibility that adrenal steroids may influence the hypothalamic secretion of ADH may implicate this area in regulation of both water and electrolyte metabolism. Concrete studies at the present time dealing with known

hypothalamic mechanisms are too few to permit definitive hypotheses. However, on the basis of existing evidence, certain theoretic considerations of possible significance for future investigation appear justified; these may, of course, be easily altered or discarded as fact emerges from sheer speculation.

The functions of the glands of internal secretion may be roughly divided into those necessary for maintenance of physiologic activities of the body and certain auxiliary mechanisms for increased endocrine activity to preserve homeostasis in the face of injury or disease. Thus, certain basic hypothalamic-endocrine rhythms probably exist which are ordinarily sufficient for maintenance of normal sodium and water balance. Fundamentally protective emergency measures for rapid or prolonged modification of the fluid environment may become activated but may lead to serious disorders in sodium and water metabolism if unchecked.

A concept recently raised by Walker[123] draws an analogy between the nucleus of the third cranial nerve and the supra-optic nucleus. The basic activity of the nucleus of the third nerve is to constrict the pupil, but fibers from higher centers are thought to inhibit the nucleus and promote pupillary dilatation; removal of these inhibitory impulses restores constriction of the pupil. Perhaps cortical inhibitory fibers similarly depress the activity of the supra-optic nucleus, but when cortical depression is induced by sleep or anesthesia, basic nuclear activity is allowed to resume and leads to antidiuresis. According to this viewpoint, sedatives and anesthetic agents may not act directly on the hypothalamus but may mimic direct nuclear stimulants by removing inhibitory impulses entering the hypothalamus from higher centers. Similar reciprocal inhibition between parasympathetic and sympathetic activities of the anterior and posterior portions of the hypothalamus, respectively, has been postulated[63], the resultant peripheral effects being determined by the dynamic equilibrium between two opposing forces.

On the basis of these fundamental neural rhythms, my own conception of possible ways in which the hypothalamus may regulate water and sodium metabolism in health and disease is schematically represented in the accompanying diagrams (Figs. 1 and 2). Possible pathways from the central nervous system to the renal tubule mediating the rhythmic excretion of sodium and water observed in healthy subjects are shown in Fig. 1. A reciprocal relation between secretory rhythms of adrenal steroids and ADH is postulated, the adrenal cortex being dominant during the day and the neurohypophysis reaching maximal activity during sleep. However, since the adrenal cortex wakes up before the cerebral cortex, subcortical or hypothalamic centers may initiate this activation, and results of stimulation of anterior hypothalamic[89] and septal areas[55] in man suggest the existence of such centers. The diurnal rhythm of adrenal cortical secretion[64,79,86] is probably dependent on rhythmic secretion of corticoid-releasing factor (CRF)[102] from the hypothalamus. Possibly, polypeptide secretion may be altered by slight changes in neural stimulation of this area, leading to elaboration of predominantly CRF-type hormones during periods of increased metabolic activity and to secretion of vasopressin-like polypeptides when water conservation is of paramount importance, as during sleep.

Increased secretion of hydrocortisone and depressed secretion of ADH may promote the increased sodium and water excretion typical of daytime activity in normal man. The ris-

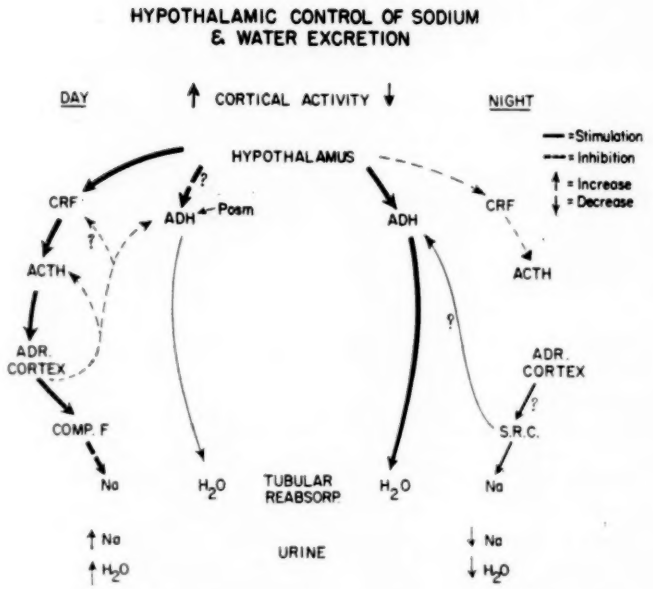

Fig. 1.—Pathways of stimulation, depicted as solid arrows, are graded in intensity, the broader, darker lines representing dominant impulses, the lighter lines less forceful stimuli. Inhibitory impulses are similarly graded and appear as dashed arrows. Question marks are appropriately placed to indicate hypothetical pathways. C.R.F. = corticoid-releasing factor; Posm = plasma osmotic pressure; S.R.C. = sodium-retaining corticoid.

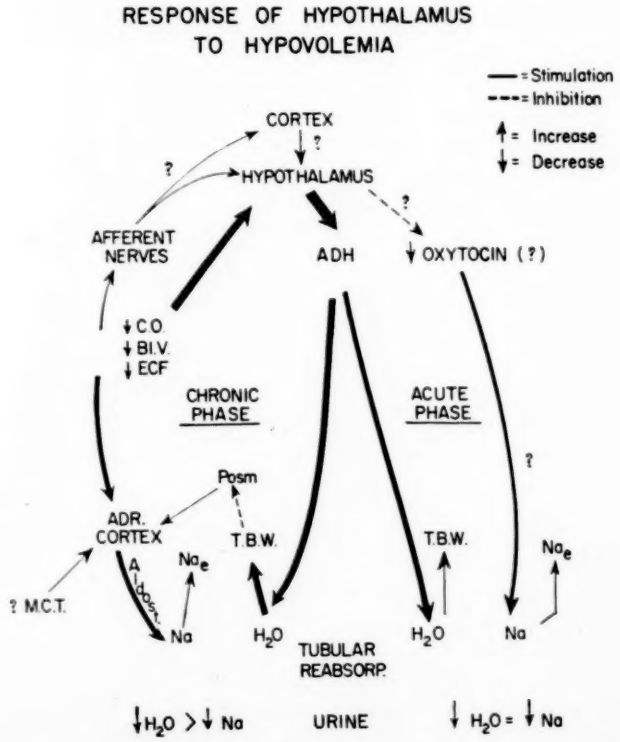

Fig. 2.—C.O. = cardiac output; Posm = plasma osmotic pressure; T.B.W. = total body water; Na = total body sodium; M.C.T. = mineralo-corticotrophin.

ing level of hydrocortisone in the blood reciprocally suppresses ACTH secretion and may also maintain a tonic inhibitory influence on secretion of ADH from the hypothalamus. If the hypothesis is correct that osmoreceptor response is mediated through the posterior lobe of the pituitary body, secretion of stored ADH from this area in accord with osmotic changes may continue despite central nuclear inhibition and provide a means of controlling water excretion independent, in a sense, of the hypothalamus. Increased hydrocortisone secretion may be related to normal daytime natruresis as a result of 1) direct inhibitory effects on renal tubular reabsorption of sodium[27], 2) antagonism of the tubular effect of salt-active corticoids[27,42], 3) increased flow of urine through the distal tubule secondary to decreased ADH action, which produces loss of sodium and water, or 4) rhythmic changes in extracellular fluid volume, which independently alter reabsorption of sodium.

A decline in CRF secretion occurs as the day wanes and is soon followed by decreased cerebral activity and, finally, sleep. An alteration in hypothalamic function, either mediated through or associated with decreased cortical and subcortical activity, may then permit resurgence of a basic hypothalamic rhythm, leading to increased neurohypophyseal secretion, decreased gluco-corticoid output, and the well-documented nocturnal decline in sodium and water excretion. Diminished secretion of Compound F may decrease steroid inhibitory effects on the neurohypophysis, with resultant ADH secretion through hypothalamic impulses which may not be strictly under osmoreceptor control. Such an occurrence may help to explain the well-documented decrease in diuresis observed during water-loading studies performed at night[85]. The decline in corticotrophic stimulation of hydrocortisone and corticosterone secretion may permit basal secretion of more potent salt-retaining steroids to dominate the kidney and not only augment sodium retention but also possibly increase sensitivity of the neurohypophysis to stimuli and thus enhance nocturnal retention of both sodium and water.

Figure 2 depicts my own concept of the means by which the hypothalamus may be implicated in formation of edema. This hypothesis is based on the viewpoint that "hypovolemic" impulses represent stresses of the first order, having priority over most stimuli that reach the hypothalamus, and "volume receptor" activity is known not to be easily suppressed in patients with circulatory insufficiency. Although acute decreases in circulatory volume lead to prompt retention of sodium and water, gradual circulatory failure may create stepwise adjustments in endocrine activity to protect the integrity of the internal fluid environment.

The hypothalamus may be able to cope with both situations by mobilizing intrinsic emergency defensive mechanisms to meet acute needs and, subsequently, modifying other secretory organs directly or indirectly to reinforce such adjustments. Since neurohypophyseal hormones are quickly released with hypothalamic stimulation and since they act promptly and directly on the kidney rather than through other endocrine glands, they would seem to satisfy the requirement for emergency protection. Prompt retention of water and, if the stimulus is strong enough, even pronounced oliguria may result.

Simultaneous stimulation of neural pathways from the brain to the kidney can potentiate antidiuresis by decreasing renal circulation, and retention of sodium may be produced by a combi-

nation of sharp decreases in glomerular filtration rate and continued tubular activity, possibly augmented by a decrease in urinary flow through the tubules. This retention of sodium may not require increased adrenal cortical secretion, and the relatively slow action of adrenal steroids on sodium excretion would corroborate the impression that acute changes may be mediated directly through neural and hormonal impulses from the hypothalamus to the renal tubule.

The hypothalamus may also participate in acute retention of sodium by altering the quality of neurohypophyseal secretion in response to hypovolemic stimuli. Increased vasopressin and decreased oxytocin discharge may lead to retention of water and sodium by removal of a natural stimulus for excretion of sodium[13]. This emergency mechanism may be activated by many experimental methods of stimulating volume receptor activity, such as postural changes, phlebotomy, and venous congestion, and may suffice when such stimuli are short-lived. However, persistence of the acute disorder in circulation or gradual but unremitting circulatory failure probably represents a constant tonic stimulation of the hypothalamus, perceived as a need for more prolonged and powerful retention of sodium and water, which may lead to widespread alteration in endocrine activity. With chronic circulatory insufficiency, enhanced secretion of ADH may initially produce relatively greater retention of water than of sodium and hypotonicity of the body fluids, which may not be offset by suppression of the neurohypophysis as a result of relatively weak osmoreceptor impulses. The pattern of adrenal cortical secretion may subsequently undergo a change to reinforce sodium retention, and increased production of aldosterone by intrinsic adrenal mechanisms in response to hypovolemia as well as hypotonicity may help restore "effective" volume and osmotic pressure. The combination of high levels of aldosterone and continued ADH discharge may then facilitate retention of ECF by the kidney and, ultimately, lead to formation of edema.

Accumulation of extracellular fluid, however, may restore circulating volume sufficiently to decrease the activity of the supra-optic nucleus and the adrenal cortex. This will lead to the "steady state" occasionally observed in edematous patients, in which mechanisms for diuresis of administered salt or water improve or even approach normal limits. Attempts at removing the fluid with diuretic agents, however, may be vigorously combatted by a return of volume receptor activity during diuresis. This theory is obviously tenuous, since little is known of the temporal relations between retention of water and that of sodium in early circulatory insufficiency. Some evidence, however, suggests that cardiac compensation is associated with diuresis of a hypotonic fluid, so that retention of water may exceed that of sodium during circulatory failure[80]. Furthermore, elevated levels of aldosterone are not consistently observed in moderately edematous subjects[72] and generally reach abnormally high levels only when low salt diets or vigorous diuretic therapy introduces salt deprivation. These observations would support the hypothesis (suggested by C. Thorpe Ray) that increased secretion of aldosterone occurs relatively late in the sequence of events descriptively labeled "circulatory failure."

An additional pathway from the hypothalamus to the adrenal cortex may be activated by the same hypovolemic stimulus leading to increased ADH secretion, that is, release of mineralo-corticotrophic hormones by a

constant hypothalamic drive that promotes secretion of large amounts of aldosterone. Although this attractive concept may permit more plausible integration of hypothalamic volume receptors and the adrenal cortex, much confirmatory evidence must be accumulated before it can be accepted.

Therapeutic Implications. Many of the conjectures in the foregoing sections on possible neuro-endocrine pathways that regulate sodium and water excretion in man will require considerable experimentation before therapeutic applications can be determined. Nevertheless, sufficient evidence exists to permit some tentative conclusions that may prove useful in clinical practice.

Clinical measures are available to lessen the retention of sodium and the edema that frequently complicate use of large doses of adrenal steroids. Retention of sodium may be minimized by low salt diets, administration of potassium, or periodic diuretic therapy. The recent availability of potent anti-inflammatory steroids which produce little, if any, retention of sodium, such as prednisone and prednisolone, has caused these agents to replace other measures in many instances.

Drugs that suppress production of adrenal salt-retaining hormone may be useful in management of edematous subjects. Recently, Amphenone (3,3,-bis [p-aminophenyl]-butanone-2 dihydrochloride) has been shown to arrest synthesis of adrenal steroids[99] and to suppress secretion of aldosterone in patients with edema and "secondary aldosteronism"[97]. Moderate sodium diuresis, apparently related to suppressed secretion of this steroid, has been described in patients with cardiac failure[97] and cirrhosis and ascites[129]. In recent studies in this laboratory[28], Amphenone produced moderate sodium diuresis in patients with mild cardiac edema but little, if any natruresis in those with advanced disease. However, this compound appears to restore the efficacy of mercurial diuretics in patients previously refractory to such drugs. Possibly, suppressed production of aldosterone permits drugs that act at other sites (the renal tubule, renal circulation, or volume regulators) to exert their classic diuretic effects. This would imply that increased production of aldosterone may accompany, rather than actually mediate, far advanced cardiac failure and that extra-adrenal mechanisms for sodium retention must also be suppressed to mobilize edema fluid effectively. These preliminary studies suggest that drugs similar to Amphenone may be useful adjuncts in diuretic therapy of far-advanced edematous patients.

An understanding of the diverse factors that promote ADH secretion is essential for proper administration of fluid therapy, in general, and of diuretic programs in edematous patients. The prolonged antidiuresis seen in many patients postoperatively[81], particularly in those with circulatory insufficiency who have had cardiac operations[126], makes even ordinary fluid replacement extremely hazardous, since severe hyponatremia and water intoxication may result. The superimposition of surgical trauma on circulatory insufficiency probably leads to such pronounced hypothalamic stimulation and persistent ADH secretion as not to be influenced by the relatively mild inhibitory effect of hypotonicity alone[49]. Amelioration in such instances has been achieved by simple, rigid restriction of fluid intake until excretion of water resumes normal levels[126].

Recent use of total hypophysectomy for treatment of many serious disorders[75,76] has resulted in increased incidence of diabetes insipidus in the

general hospital population. Although this disease is generally considered benign and easily managed with Pitressin, water intoxication, mental torpor, vomiting, profound hyponatremia, and abdominal cramps may sometimes follow vigorous Pitressin therapy and overzealous fluid administration. The paradoxic sodium diuresis associated with administration of Pitressin in the face of large fluid loads[70] may be responsible for some of these symptoms.

Physiologic studies of neurohypophyseal function in hypophysectomized patients[29] have provided some information that may permit avoidance of such complications. The simple precaution of severing the pituitary stalk close to the diaphragma sellae and gently retracting the proximal portion to one side, without cauterization, permitted satisfactory removal of anterior pituitary tissue for the desired effect on neoplastic growth. At the same time, the postoperative incidence of diabetes insipidus was significantly lessened probably by preservation of some hypothalamic neurosecretory tissue. Two of the patients in whom diabetes insipidus developed postoperatively suddenly became refractory to Pitressin therapy, whereas polyuria had previously been well controlled. In one patient, allergy to the oily vehicle for Pitressin tannate was suspected and use of another menstruum restored sensitivity to the drug. In the second patient, severe hypercalcemia from metastatic involvement of bone was detected during the period of resistance to Pitressin; with appropriate irradiation, levels of serum calcium returned to normal and Pitressin again became effective.

Since the upright position immediately initiates intracranial volume receptor activity, proper positioning of patients during diuretic therapy is important for maximal efficacy of these drugs. The recumbent position should not only lessen hypothalamic antidiuresis but also permit better mobilization of dependent fluid for removal by the kidney. Let us now consider the possible ways in which persistent neurohypophyseal secretion during diuretic therapy may lessen the desired removal of edema fluid from the body. The persistent action of ADH on reabsorption of solute-free water during sodium diuresis will lead to excretion of a fairly hypertonic urine in most instances, although at high rates of flow, osmolarity is likely to decline toward the isosmotic level[130]. Excretion of sodium in hypertonic urine is not unusual during diuretic therapy of far-advanced edematous patients, and continued removal of sodium in excess of water may ultimately cause severe hyponatremia, cellular edema, and circulatory collapse. In such an emergency, use of a hypertonic saline solution may be imperative for survival, yet administration of large salt loads is paradoxic and only enhances formation of edema. A decline in urinary osmolarity toward the isosmotic level during sodium diuresis is desirable, since this would reflect greater loss of water than sodium, effected by continued extrarenal loss of water in the form of insensible perspiration.

In some patients, loss of sodium from the body may result in suppression of neurohypophyseal activity through osmoreceptor impulses, and proportionate water diuresis may accompany the sodium diuresis. In far advanced circulatory insufficiency when, according to my hypothesis, hypovolemic stimuli are relentlessly driving the supra-optic nucleus to secrete ADH, changes in osmotic pressure may not effectively suppress the neurohypophysis, and maximal retention of water during sodium diuresis

may set the stage for hyponatremia and intracellular edema.

Greater awareness of the participation of the neurohypophysis in production of oliguria[66] and edema may suggest measures to suppress the secretion of this gland and thus permit more intelligent management of seriously ill, edematous subjects. Unfortunately, potent inhibitors of the neurohypophysis are few, but gluco-corticoids, such as hydrocortisone and prednisone, which may produce sodium and water diuresis in normal subjects[27], may also promote sodium diuresis in some cardiac patients[101]. A suppressive effect of adrenal steroids on ADH release[30] may explain the increased water diuresis associated with their administration to patients with cardiac failure[68]. Adrenal steroids may even potentiate the action of drugs that promote sodium excretion[102]. The fact that ethyl alcohol only occasionally enhances excretion of water in edematous patients[65] indicates that this substance exerts only mild inhibitory effects on the neurohypophysis[22,47,48].

Knowledge of the many substances that stimulate ADH secretion may prevent therapeutic errors caused by fortuitous suppression of the effect of diuretic agents. In this regard strict avoidance of many narcotics, sedatives, and hypnotics, as well as acetylcholine type compounds and excessive smoking, within at least a few hours of initiation of diuretic therapy, may improve the response by removing a potent neurohypophyseal stimulant. The influence of hypovolemia on the hypothalamus may prevent satisfactory removal of edema fluid by yet another means than through the neurohypophysis. This pathway involves the occasional occurrence of thirst during diuretic therapy, which is probably mediated through contraction of fluid volume and is perceived as a dehydrating stimulus in anterior hypothalamic thirst centers. Since these subjects are generally allowed water freely, they will frequently drink a volume of tap water nearly equal to the volume of urine removed by action of the diuretic compound. This phenomenon explains the perplexity of the physician who notes considerable diuresis without associated weight loss! Obviously, this compensatory reaction of the body should be thwarted by restriction of fluids during diuretic therapy to avoid hyponatremia and water intoxication.

Although all significant factors could not be covered in this discussion, these remarks, it is hoped, emphasize the importance of basic physiologic knowledge for intelligent management of clinical problems in sodium and water metabolism. Further investigation of pathways to and from the hypothalamus may help clarify the endocrine control of sodium and water metabolism and ultimately lead to better understanding of the pathophysiologic aspects of the formation of edema and thus to more adequate therapeutic measures.

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SUMMARIO IN INTERLINGUA

(See page 67 for original article)

Le Resultatos Del Tractamento De Statos Psychotic Per Medio Del Plus Recente Compositos De Phenothiazina Que Es Efficace In Micre Doses

Quatro compositos de phenothiazina, relationate a chlorpromazina, esseva investigate relative a lor efficacia in le tractamento de statos psychotic. Le numeros del patientes usate esseva significative: 667 in le caso de Compazina (prochlorperazina); 206 in le caso de Trilafon; 176 in le caso de Vesprina; e 94 in le caso de Winthrop #13.645–5. Omne le patientes esseva asylatos in un hospital mental del stato e suffreva de psychoses chronic. Le differentias principal inter le presente compositos e le previemente introducite derivatos de phenothiazina, *i.e.*, per exemplo, chlorpromazina, promazina, e mepazina, es (1) lor plus intense activitate pharmacologic e therapeutic e consequentemente lor plus basse nivellos de dosage e (2) le facto que lor uso resulta multo minus frequentemente in le occurrentia de effectos lateral e de complicationes toxic. Importantissime es le absentia de jalnessa post le uso de iste drogas e, in le series usque nunc studiate, le absentia de agranulocytosis. Iste drogas es etiam characterisate per le production de pauc o nulle sedation (per contrasto con chlorpromazina e reserpina), sed illos exerce un multo plus pronunciate effecto benefic super le manifestationes psychotic del typo de delusiones, hallucinationes, e statos de excitation pathologic. Le tabulation del effectos lateral monstra (1) manifestationes allergiforme, (2) effectos "trophic" e endocrin, e (3) effectos neurologic. Le signification e le tractamento de istos es considerate in detalio. Le principal effecto neurologic, *i.e.* un certe grado de parkinsonismo, es frequentemente (ben que non semper) un accompaniamento inevitabile de beneficios therapeutic in le tractamento de psychoses. Illo debe esser attaccate per le manipulation del dosage del agente therapeutic e additionalmente per le uso de Cogentina. Le drogas hic discutite es specialmente efficace in le tractamento de schizophrenia, de psychoses manic-depressive del gruppo manic e etiam, synergicamente con electro-choc, del gruppo depressive, e de delirio organic. Le drogas representa clarmente un passo in avante in le tractamento pharmacologic del psychoses.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.
CLINICAL PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

AND

FRANK R. DRAKE, M.D.
INSTRUCTOR OF CLINICAL PSYCHIATRY, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE
DENVER, COLORADO

PSYCHOANALYSIS AND GENERAL MEDICINE

BY JAMES GALVIN, M.D.
MEDICAL DIRECTOR, COLORADO PSYCHOPATHIC HOSPITAL, DENVER, COLORADO;
ASSOCIATE PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE,
DENVER, COLORADO

IT is probably not far from the truth to say that no specialty in medicine is less understood by the general practitioner than psychoanalysis. This is in many ways unfortunate. Not the least of the misfortunes which arise from this lack of understanding is that the distance between the psychoanalyst and his other medical colleagues is increased. This distance is already too great and is certainly also contributed to by the analyst himself. Regardless, however, of where the blame lies, it seems to me that there can be no doubt that isolation from the rest of medicine is injurious to medicine in general and also to the analyst who is, after all, a physician.

It is not generally known that psychoanalysis began with a general practitioner, Joseph Breuer. Although most of the understanding, most of the theory, most of the technique which we have in psychoanalysis today must be attributed to the genius of Sigmund Freud, the first case of psychotherapy which must unmistakably be regarded as a forerunner to psychoanalysis was conducted by the general practitioner, Breuer. Breuer was a fascinating man. He enjoyed the high respect of the medical profession in Vienna and, as a matter of fact, served as the private physician for the families of many of the faculty in the University of Vienna. He was almost exclusively interested in his patients. In a country in which academic appointment is much more highly regarded than here in the United States, Breuer refused the nomination to professor, a thing almost unheard of in Germanic countries.

Breuer treated a young girl who suffered from very severe hysterical disease. She had conversion symptoms of a very disabling kind. He made the observation that when he encouraged her to talk about these symptoms, the symptoms moderated. At a later time, he used hypnosis and encouraged the girl then to talk about the symptoms under hypnosis. Without exception she tended to talk about the symptoms in an historical sense, that is, she

would trace the present status of the symptom backward towards its beginning. When this kind of reliving of the genesis of an hysterical symptom under hypnosis was carried out, it was found that the symptom moderated and then disappeared. This experience with the famous patient, called in the medical literature Anna O., but whose real name was Bertha Pappenheim, was the independent discovery of Breuer.

When Freud returned from his year in the French neurological clinics, preparing himself for the practice of clinical medicine, he learned about this case. Freud had, of course, a very extensive experience with hypnosis in the French clinics which were then the centers in the world for this kind of practice. He was very excited about Breuer's experience, attempted himself to use the same technique, with success, and from then on moved forward into the development of psychoanalysis.

Another somewhat amusing aspect of Breuer's experience has to do with the termination of this now famous case. Breuer apparently was particularly conscientious with his patient, visited her often and gave her large amounts of time. It would seem that Mrs. Breuer did not take kindly to this enterprise of her husband's and began to make that kind of wifely pressure with which most of us are familiar, with the consequence that Breuer soon decided that he would not anymore practice this method of psychotherapy. The patient's response to Breuer's announcement of the termination of her treatment was to act out with great vigor an hysterical child birth. This was just too much for Breuer and he left town for a long vacation.

In addition to the origin of psychoanalysis with a general practitioner, it must also be said that doctors in general practice everyday make use of theoretical concepts which are similar to some of those of psychoanalysis. These generally are not so recognized by the doctor who uses them but his skill is not diminished by his lack of recognition.

For example, one of the most important contributions of the Freudian system is the idea of and the description of maturation in the psychological sense. We know, that the baby moves through various stages of development, maturing and learning as he goes and that the stages of development are perhaps most easily understood in terms of the organ system from which the baby derives maximal pleasure at any given time. We speak, for example, of the oral period during which the baby is mostly preoccupied with oral and gastrointestinal activity. It is from this system that he derives his greatest gratification and it is in the mastery of this system that he makes his greatest progress. Later on come other stages described in the same general way. We have been told about the opposite of maturation, that is, regression. Regression is usually, of course, thought of in terms of the more massive and severe regression. All of us are familiar with the idea of regression in schizophrenia. The fact is that minor regression falls within the limits of normal. For example, there are well-defined regressive satisfactions involved in our going to sleep at night. Furthermore, regression is an inevitable part of almost all organic diseases. We do not usually think of the psychological regression which accompanies an upper respiratory disease, but this regression is a fact. Let us take ourselves as examples. Under normal circumstances, we expect of ourselves to get up at a certain time of morning, perform certain duties, to expend certain energy. We must get up at 7, we must have breakfast at 8, we must be in the

hospital at 9, and in the office at 1. Now let us see what happens to this level of responsibility if upon awakening we find that we have an upper respiratory disease, clearly recognized as such. Immediately, we begin to make allowances for ourselves. We begin to excuse ourselves from responsibilities which are a normal part of our adulthood. We permit ourselves a little bit to be babied. We stay an extra half-hour or extra hour in bed. We may skip going to the hospital that day, or may cancel the appointments of patients who can be skipped that afternoon. This is regression: certainly of a minor and easily reversible sort, but nonetheless, unmistakably regression.

Let us turn from this to look at our patients who have the same kind of experience. For most patients, minor regressions such as those associated with upper respiratory disease, do not necessitate treatment by the doctor. There are, however, two kinds of patient with whom the doctor must interfere. One is the patient who regresses too far too fast with too little excuse: the individual who is accustomed when he finds himself with upper respiratory disease to spend a week in bed. With this patient, most physicians will, sooner or later, lay hands on the regression and undo it. "You have now been in bed long enough, there is no further excuse for this, get up and go back to work." Another kind of patient who must be specifically handled by the physician, is the one who denies his regressive tendencies. This man or woman with an upper respiratory disease, will not permit himself even the tiniest regressive satisfaction. He gets out of bed although on a biological pleasure-pain basis he would much prefer to be home, he demonstrates his courage, his aggressiveness and his manhood by going to the office at the same time as usual (thereupon giving his cold to everbody else), all of this being intended to deny that regression is for him a possibility. Here, too, the physician often interferes, simply by ordering the individual to stay at home for a day.

I mean this brief discussion of a kind of regression to demonstrate that this is a classical psychoanalytic, theoretical conception which is commonly used by all physicians although they do not, I think, usually recognize that they are dealing with regression.

There has been much discussion in recent years about the relationship between psychoanalysis and medicine. In other countries, lay analysis, that is psychoanalysis not conducted by physicians is much commoner than here. In this country, the professional associations have taken the position that psychoanalysis like other psychotherapies is by tradition and by law, the responsibility of the licensed physician. Franz Alexander[1] has probably been one of the loudest voices among those who fervently wish for and energetically work towards better communication between psychoanalysis and general medicine.

There can be little doubt that psychoanalysis has had an effect on medicine, even though communication has been imperfect. In this day and age, when the physician is seldom able to know the life history of the patient seen for the first time, history taking has become extremely important. The old methods of question and answer history taking with much emphasis on quantitation have been usefully modified by psychoanalysis so that it is commonplace now for the physician to ask open ended questions and then let his patient give his own account of his disease. This does not, of course, mean that quantitation does not continue to be of the utmost importance. It does not mean that questions and answers

are not useful. Neither does it mean that the patient who rambles endlessly and aimlessly ought not to be steered or stopped. Nonetheless, I think the average medical history now contains much more of the indirect method of analysis than formerly.

Gregg[2] has pointed out that we are more interested now in the natural history of disease than we were formerly and this, too, may in part come from analysis. In older times, the physician interested himself mostly in the current status of his patient. He was interested in what disease process was present now and relatively little with how this disease process began and developed. Public health, with its emphasis on prophylaxis, also deserves much credit for the change.

This brings us to the problem which we have in medicine of dealing with the hopeless patient, the patient who cannot be cured, who suffers from a chronic disease, or the patient who will inevitably die. I fear that all physicians, motivated as we are primarily towards therapy, are better defended against this kind of patient and therefore less able to bring comfort to him than we are in other cases. This comes not so much from psychoanalysis as from psychiatry which even now after much improvement during the last 50 years has still to deal with many patients for whom the best that can be hoped is some palliation. Medicine is beginning to relearn some responsibility and a system of techniques for dealing with the hopeless patient.

I wonder how much we have in this way contributed to our diminished popularity among our fellow citizens in general. Consider our unwillingness to attend the dying; almost no physician now keeps the death bed vigil. Of course, we have excellent reason for this, we are busy, we can do no good, and the like. I am inclined to suspect that even if these rationalizations are true as they may well be, still the families would feel much better pleased with us if we stayed longer with our hopeless patients.

There is another peculiarity in this area between general medicine and psychoanalysis which catches my interest. There can be little doubt, I think, that the unity of the total organism upon which the modern practice of psychosomatic medicine is based has received its modern re-emphasis from psychoanalysis. This principle has, of course, also been taught by other schools in other ages but in its present day version it stems primarily from psychoanalysis. The concept in practice of the unity of the organism is often more clearly grasped by general practitioners than by analysts. Unfortunately, many analysts, indeed many psychiatrists, have lost, or at least very seldom use, their basic medical skills. Meanwhile the general practitioner, the wise general practitioner, continues to treat his patient in his emotions and in his body simultaneously.

I am afraid we must all admit, to our chagrin, that there has been a considerable change in the relative affection and hostility felt for physicians by their patients in the last 30 or 40 years. We have lost much of the regard with which we were then held. The reasons for these changes are many and complicated. It is possible, however, that among the reasons are certain changes in our techniques, certain changes in the way in which we conduct our practices.

All of these changes and the many others which have taken place are necessary, are reasonable and in most cases contribute primarily to the welfare of the patient. It would be grotesque in this day and age to perform surgery at home when we have modern hospitals and modern surgical suites with

so much apparatus indended to protect the patient against pain and other complications. Nonetheless, we might consider the possibility that we have been inexpert in interpreting these changes to our patients and by our inexpertness have stimulated their hostility against us with resultant damage to our prestige and the affection and regard in which we were previously held.

Let me give an example of this. Most doctors are reluctant now automatically to make night calls for pediatric patients. There are two classes of reasons for this. The first is that very many calls in the night are alarmist, are made by parents frightened without reason. The other kind of reason is that if a child is truly ill, he can often be better and more easily treated in hospital than in his own home. Therefore, when we now are called in the night to see a sick child, we are quite apt to question the parents in some detail about the necessity of making the call. This, of course, communicates to the parents our reluctance to come, without making any communication to them about the reasons for this reluctance. This matter is further complicated by the fact that parents dealing with a sick child in the middle of the night are again psychologically regressed, in greater or lesser degree panic stricken, they are in a state in which their emotions are given more weight than usual, and their common sense less weight.

The basic principle involved here is that when people are using large amounts of psychological energy to deal with a crisis in their lives they have much less available for the sensible and thoughtful inspection of explanations. The middle of the night is no time for the explanation. The parents are at such times much less reasonable than they are under ordinary circumstances. It would, therefore, seem sensible that doctors make a point of explaining their practices and their reasons for doing things in this way to their patients in advance of the acute need. This idea, of course, is not new but has been widely preached in medical societies in all parts of the country. We may be causing unnecessary difficulty for ourselves, earning unnecessary hostility, because we have failed adequately to understand the laws of emotions by which patients and the families of patients inevitably operate. A better understanding of the emotionality of these lives might well make general practice easier. The most fertile source of such understanding, at the present time, is psychoanalysis.

Psychoanalysis has been defined as that method of research and therapy which makes use of the following concepts: 1) the unconscious; 2) transference; 3) free association and 4) resistance. Let me go over these things and briefly define them.

First the unconscious. There is a large part of the mind in which wishes, fears, memories can exist without being available to the introspection of the individual. The contents of the unconscious mind can never be known directly. They can be known only derivatively. These things may not be conscious, but they make themselves known in effects they produce, in symptoms, some of them so simple as the slip of the tongue, others much more serious. Above all, they make themselves known in dreams.

Here we must consider the phenomenon of the mother who claims that she loves her child perfectly and never gets angry at her, but complains of dreams in which her child is repeatedly suffering catastrophes. The general practitioner knows about and uses his knowledge of the unconscious. He knows that his patient often cannot tell the physician everything about himself. He knows that he must make certain as-

sumptions about the patient, unsupported by direct evidence. The physician has learned to watch, for example, the body language of his patient. He may not realize that he is making observations of unconscious material but he is certainly aware of it when a patient, who is describing her love for a child, clenches her fist and beats it on the desk allegedly to emphasize her point.

Transference is usually defined as acting towards a second person in a way which was learned in relation to an earlier significant person, this being done without conscious recognition on the part of the person who is doing it. Thus, if a patient has learned to fear his father, he will have a tendency to fear other father-like people (among whom is often the doctor) without knowing or even examining whether or not fear is reasonable in the second situation. This again usually not called by this label, perhaps not recognized as such, is still used by the wise practitioner of general medicine. All of us, have learned to shake in our boots in the presence of the patient who says, my last doctor was a very bad man, he was ignorant, unsympathetic, dishonest and immoral, but you doctor, I know are different. We have learned from bitter experience that when a transference of this sort is made once it is probably made again and that in spite of the fact that our own wickedness and ignorance may not immediately be apparent to the patient, sooner or later, he comes to the perception of them.

Free association is, of course, the technique in analysis of expecting the patient to report every thought that comes into his head without censoring, without sorting them out, without discarding anything. Free association obviously is a kind of ideal which is approached but not reached. We have already spoken of the related form of free association used in general medicine. This is the open ended question, the permission given to the patient to talk on about his own disease, without direction, without interruption for comfortable and reasonable lengths of time.

In psychoanalysis, we are of necessity interested in the resistances which a patient has to many psychological phenomena: to the recovery of a memory, to the discussion of a subject, to the giving up of a life pattern, to many other kinds of things. The general physician is also painfully aware of this propensity of all human beings. General physicians are not usually so concerned with resistance in the purely psychological sense as they are with psychological resistance within medical discipline. Who has not struggled with a diabetic patient who refuses to stay on his diet or refuses to take his insulin or who refuses to attend to the insulin dosage ordered by his physician and insists on writing bizarre prescriptions for himself? We know the tuberculous patient who will not or cannot cooperate, we know the peptic ulcer patient who cannot avoid irritating foods, we know many other patients who for one reason or another have great, sometimes insurmountable resistance to a sensible medical regimen. All of us have been accustomed from our earliest medical days to deal with these resistances. Certainly in our dealings with them we often fail, but we have developed techniques, and these are in part similar to the techniques used by the analyst, to overcome the resistance.

We attempt, for example, to explore the nature of the resistance, so that reason can be brought to bear on it if it is delusional. We use persuasion, we use authority, we use many psychological maneuvers to deal with resistance in general medicine in precisely the

same way as these things are done in psychoanalysis, without ever recognizing the similarity of the maneuvers in the general field and in the specialty.

All of these things are of the greatest importance because of the number of psychiatric patients with which every general practitioner and every other practitioner of medicine must inevitably deal. I would certainly hope that the practice of psychiatry by the general practitioner within his limits would become much more formalized, much more clearly recognized. Communication between us is of the greatest importance so that the general practitioner can do as much as possible with the problems which he must face.

To sum up, I have attempted in these few words to bring to your attention, the unnecessary and damaging imperfection of communication between general medicine and psychoanalysis. Psychoanalysis had its origin in general practice and with a general practitioner. There are distinct similarities between some of the technical maneuvers which are described in psychoanalytic literature and generally thought of as a part of psychoanalytic technique and those commonly used by general practitioners, who may not recognize the similarity of what they do to what the analyst does.

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SUMMARIO IN INTERLINGUA

(See page 43 for original article)

Le Transporto De Acido Uric In Le Sero

1. Acido uric es presente in sero in duo formas: libere e ligate a albumina.

2. Le affinitate de acido uric pro albumina seral differe inter seros normal e pathologic.

3. Post incubation con uricase, ultrafiltrato seral produce un plus grande residuo de chromogeno que le sero original.

PHYSIOLOGY

PPOCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF OCTOBER 15, 1957

INFORMAL SEMINAR ON ESSENTIAL HYPERTENSION

Introductory Remarks. CHARLES C. WOLFERTH, M.D. (Department of Medicine, University of Pennsylvania). The term "Essential Hypertension," irrespective of its etymologic connotations, has, by common usage become a blanket designation applied to more or less sustained elevated systemic arterial blood pressure whenever the cause or causes remain unknown. The term is unfortunately still applicable to the vast majority of instances of elevated arterial pressure.

In this country, essential hypertension is the second most devastating physical disorder to which the population is subject, being outranked by atherosclerosis only. Indeed, there are reasons for believing that it aids atherosclerosis in achieving its unenviable position. It presents knotty problems in the fields of physiology, including neurophysiology, pathology, biochemistry, pharmacology, internal medicine in general and some of its sub-specialities in particular, neurology, psychiatry and surgery. There is perhaps no other subject of medical interest with such a voluminous literature pertaining to it.

We have learned much concerning hemodynamics and its neurogenic and hormonal controls relevant to blood pressure levels but there are still gaps in our knowledge large enough to handicap attempts to formulate useful hypotheses concerning blood pressure regulation, to say nothing of its derangements. Nevertheless, there have been advances in the treatment of hypertension in recent years which have helped to answer some of the questions that troubled us in the past but which at the same time have presented new problems. Our essayists this evening will deal with certain interesting aspects of the current situation.

Relationship of Hypertension to Steroid Formation by Incubated Human Adrenal Tissue. DAVID Y. COOPER, M.D., JOSEPH C. TOUCHSTONE, PH.D., JOHN M. ROBERTS, M.D., AND OTTO ROSENTHAL, M.D. (Department of Surgery, University of Pennsylvania School of Medicine). Steroid production by incubated human adrenal slices has been studied as previously described (Fed. Proc., 14, 196, 1955) in 8 patients with metastatic carcinoma and 23 patients with hypertension. Paper chromatograms for semiquantitative estimation of steroids were divided into before F, F, "E", B + S and Δ^4 androstene-11β 01-3, 17-dione areas. Adrenal incubates and adrenal venous blood obtained at adrenalectomy showed similar steroidal chromatographic patterns. Approximately one-half of the incubates from hypertensive patients formed significantly more hydrocortisone per gram of tissue than those from carcinoma patients. The remaining half of the hypertensive incubates formed approximately the same amount of hydrocortisone as the carcinoma incubates. The steroids of the B + S position were significantly elevated in all hypertensive incubates studied. When hydrocortisone formation in micro-

grams per gram of tissue was compared to diastolic blood pressure, a significant negative correlation ($r = -.693$) was found. Increased eye ground changes, albuminuria and Smithwick Grouping were all similarly related to a decrease in hydrocortisone formation (μg./gm./24 hrs.). In hypertensive incubates, the ratio of F to B + S (1.6 — 1.1) was lower than that of carcinoma incubates (2.5). These findings suggest that with increasing severity of hypertension there are changes in the ratio of steroids formed.

Pharmacologic Actions Suggestive of Etiologic Mechanisms in Essential Hypertension. JOHN R. BEEM, M.D. (Department of Medicine, Hahnemann Medical College). Although the pathologic physiology underlying most cases of hypertension is unknown, the importance of the nervous system in maintaining elevated blood pressure is demonstrated by certain pharmacocologic observations. Drugs which depress impulses at various points along sympathetic pathways from the higher centers to the neuroeffector sites have been shown to exert antihypertensive action. Blood pressure has been controlled even in severe essential or malignant hypertension, in acute and chronic nephritis, renal artery occlusion (the clinical counterpart of the Goldblatt kidney) and toxemias of pregnancy. In contrast, ganglion blockade not only fails to protect against, but may intensify the hypertensive response to norepinephrine. It appears that vasopressor activity of renal origin may be mediated in part through the sympathetic nervous system. Systemic hypertension, renal ischemia and vascular damage may be intensified and a vicious cycle created. The importance of the nervous system in the initiation and progress of hypertension is suggested.

The influence of this system is known to be greatly modified by fluid and electrolyte balance and distribution. Sharply restricted sodium intake, natriuresis and adrenalectomy exert antihypertensive effect and intensify the vasodepressor effect of pharmacologic or surgical sympathetic interruption. The limited application of rigid salt restriction, potentially toxic or inconsistently effective diuretics has led to a continued search for a more rational augmentation of antihypertensive action. Recently a nonmercurial drug, chlorothiazide, when given orally has been shown to enhance the excretion of sodium and chloride equivalent to intramuscular organomercurials. Administered to 27 hypertensive patients whose blood pressure was previously controlled by a combination of reserpine and mecamylamine, it was possible to reduce the dose of ganglion blocker by one-half, diminish side effects thereby, and maintain control of blood pressure. Thus, chlorothiazide may prove useful in further elaborating the complex interrelations in the initiation and progression of hypertension.

The Effect of Antihypertensive Agents on Vascular Deterioration in Patients with Hypertension. JOHN H. MOYER, M.D. (Chairman, Department of Internal Medicine, Hahnemann Medical College and Hospital). The question is frequently raised as to the beneficial effect of blood pressure reduction in patients with essential hypertension. Elevated blood pressure notoriously is associated with vascular deterioration in three important vascular beds, namely, the brain, the heart and the kidney. Using one of these areas as an index for the vascular effect of hypertension, observations have been made on renal hemodynamics including glomerular filtration rate and renal blood flow. The study was divided into two parts (1) observations on the renal status in a

group of 133 patients presenting themselves to the Clinic without previous therapy and (2) the vascular effect of blood pressure reduction on patients who were followed for 2 years or more with antihypertensive therapy. The latter patients were compared to a similar group of individuals who did not receive antihypertensive therapy. Observations on renal hemodynamics were made before therapy was begun and 2 to 5 years following institution of therapy. Clinical results indicate that the reduction in blood pressure was accompanied by a significant overall decrease in both morbidity and mortality. The observations on renal function relative to treatment indicate that the patients fell into two groups, those with mild disease (control diastolic pressure less than 130 mm. Hg) and those with severe disease (diastolic pressure more than 130 mm. Hg). In the patients with mild hypertension, renal vascular deterioration was not significantly different in the untreated patient from that in patients who were treated. However, in the patients with severe disease, renal vascular deterioration progressed quite markedly over a 2-year period when untreated. Treatment had a definite protective effect in arresting vascular deterioration, in that the glomerular filtration rate and renal blood flow following therapy in the treated group were exactly the same after 2 years of therapy as they were prior to the induction of therapy. However, renal function did not improve, indicating that when renal damage already exists, therapy arrests the disease but does not return renal function towards normal. The important therapeutic conclusion is that blood pressure reduction *per se* is the important factor in arresting vascular deterioration. Methods for reducing blood pressure are unimportant just so long as they are effective. Therefore, surgical approaches, ganglionic blocking agents, centrally acting agents, low-salt intake and psychotherapy may all have definite beneficial effect as long as the blood pressure is lowered effectively.

BOOK REVIEWS AND NOTICES

CORONARY HEART DISEASE, ANGINA PECTORIS —MYOCARDIAL INFARCTION. BY MILTON PLOTZ, M.D., Clinical Associate Professor of Medicine, State University of New York. Pp. 353; 107 ills., 28 tables. New York: Paul B. Hoeber, Inc., 1957. Price, $12.00.

THIS is a very competent presentation of a topic of greatest importance. The underlying philosophy is that we are dealing with a disease that is susceptible of study with regard to cause, treatment, and possible prevention. Everyone will agree that there are many disputable points, such as the dietary management or the use of anticoagulants and the author gives a fair presentation of varying opinions and does not hesitate to express his own clinical judgment. The reviewer enjoyed particularly the chapters on lipid metabolism, on case reports, on differential diagnosis, and on the medicolegal aspects. While the author presents all the operative procedures that have been recommended, one can only fully agree with his statement that the place of surgery in the treatment of coronary artery disease is far from settled. There are many references to guide the reader further, it being obvious that the literature is full of contradictory statements.

H. R.

ENZYMES, ANTIGEN AND VIRUS. BY SIR MACFARLANE BURNET, Director of the Hall Institute for Medical Research, Melbourne, Australia. Pp. 193; 8 ills. New York: Cambridge University Press, 1956. Price, $3.50.

MOST immunologists are familiar with Burnet and Fenner's "Production of Antibodies" in which in 1949 they put forth the self-marker concept and the hypothesis that antibody is produced by a replicable adaptive enzyme mechanism. These important immunologic ideas attracted widespread attention, and they engendered much research, the results of which established the self-marker as an immunologic principle but denied the adaptive enzyme idea.

In one sense the present volume is a second edition because it again includes the subject of antibody production, this time with the development of a new concept, labelled *genocopy*, that is based upon current understanding of protein synthesis. But this volume is more than a second edition. Sir MacFarlane is quite taken with the possibility that the self-marker bears an important relation to tumor transplantation and carcinogenesis. Finally, and most effectively, he describes the multiplication of influenza virus drawing attention as he does so to a property he considers to be common to adaptive enzymes, antibodies and influenza virus. They are all, he says, abnormal functional proteins synthesized by RNA macromolecules which "remember" and pass on "information" within the cell in a type of limited inheritance.

The fact is that this time Dr. Burnet has covered about four times more immunologic territory than he and Fenner did in the 1949 edition, and in this reader's opinion he will stir up that much more discussion and controversy. This is all to the good because disbelief is a powerful incentive to research.

Unlike "Production of Antibodies," many sentences are awkwardly arranged and difficult to understand. a situation suggesting that a final rewriting would have been desirable. Nevertheless, this is a contribution to the biologic literature of the first magnitude, and all students of immunology should read what one of the great minds in human biology has to say.

E. S.

SURGERY IN WORLD WAR II. ORTHOPEDIC SURGERY IN THE EUROPEAN THEATER OF OPERATIONS. Edited by COL. JOHN BOYD COATES, JR., MC, MATHER CLEVELAND, M.D., AND ELIZABETH M. MCFETRIDGE, M.A. Pp. 387; 86 ills. Washington: Office of the Surgeon General, Department of the Army, 1956. Price, $4.00.

THIS text, since it is in the nature of a report, is not heavily illustrated. It will serve as a constant reference book for members of the Medical Corps of the Army and Navy as well as the Administrative Corps of the Medical Department. The conclusions relevant to the management of fractures and dislocations are excellent and are based on reports from 15 Evacuation Hospitals, 24 General Hospitals and 61 Station Hospitals.

Phases of the text, especially the administrative considerations should be included in medical school teaching, especially in this era of mass casualty concern from thermonuclear weapons.

This is a very worthwhile text and it left the reviewer comforted to learn of the excellent and skillful care the "G.I." received during World War II. A. S.

HERZ- UND GEFÄSSERKRANKUNGEN. NEUE WEGE EINER FUNKTIONELLEN DIFFERENTIALDIAGNOSE. By R. VÖLKER, City Hospital Bad Oeynhausen. Pp. 168; 106 ills. Darmstadt: D. Steinkopff, 1957. Price, paper $7.77; cloth $8.25.

DIMINUTION of the functional capacity of the heart and arterial system is studied by the relatively simple photoelectric, thermoelectric, and gasanalytic methods. The volume pulse, determined at the tips of the fingers or toes, is a highly sensitive test, and this is demonstrated for functional and organic vascular diseases, and for coronary insufficiency; alternating pulse, and the variations observed with premature beats and with atrial fibrillation are discussed. Spontaneous rhythmicity of the peripheral circulation in health and in obliterative endangiitis is described, as well as the behavior of the peripheral pulse in neurocirculatory dystonia, and the changes brought about by thermic stimuli. The frequency of changes in the very periphery of the vascular system in association with myocardial infarction and angina pectoris is pointed out. Photoelectric determination of the O_2 content of the peripheral blood does not inconvenience the patient and when simultaneously respiratory function (O_2 and CO_2 content) is determined, and when a 10% O_2 breathing test is used, cardiac and pulmonary insufficiency can be reliably determined, sometimes when clinical, radiologic and electrocardiographic data are still normal. The technical methods used are described in a special chapter. H. R.

BLOOD AND BONE MARROW PATTERNS. By G. D. TALBOTT, M.D., ELMER R. HUNSICKER, B. S., AND JONAH LI, M.D. Pp. 59; 145 ills. in color. New York: Grune & Stratton, Inc., 1957. Price, $12.00.

THIS atlas consists of a series of color plates which depict the various blood cells in both normal and abnormal patterns. Unfortunately, a number of the reproductions are of poor quality and do not clearly illustrate the features which the authors are attempting to indicate. The better plates may be useful, however, in the teaching of pertinent aspects of hematology. C. Z.

VITAMIN B_{12} AND INTRINSIC FACTOR 1. EUROPÄISCHES SYMPOSIUM HAMBURG 1956. Edited by H. C. HEINRICH, Physiologisch-Chemisches Institut der Universitat Hamburg. Pp. 575; 421 ills. including 1 in color. Stuttgart: Ferdinand Enke, 1957. Price, DM 79.

AN effort at integration of the extant knowledge of vitamin B_{12} has met with remarkable success in this well illustrated volume. Among the 62 contributions included are several dealing with the biological and biochemical aspects of vitamin B_{12}; the stereochemical structure of the vitamin and its components are described by Smith, Folkers, and Hodgkin. The occurrence and isolation of analogues of vitamin B_{12} are discussed; a relationship between riboflavin and cyanocobalamin is of considerable interest. A section of the conference is devoted to intrinsic factors and vitamin B_{12}-binding substances. Purified preparations of the intrinsic factor have been studied extensively and chemically characterized. A stoichiometric relationship appears to exist between the vitamins and intrinsic factor. Additional sections deal extensively with the assay of vitamin B_{12}, manifestations and pathogenesis of B_{12} deficiency, tissue distribution, metabolism, and therapeutic applications of this factor. While the majority of the reports are published in English, there are many in the German language which may be a disadvantage. However, the contents testify to the vast amount of work being done in this field and offer many challenges for the future. C. S.

PREVENTION ET TRAITEMENT SPECIFIQUES DE LA TUBERCULOSE. By LEOPOLD NEGRE, Pasteur Institute. Pp. 242. Paris: Masson et Cie, 1956. Price, 1.800 fr. (about $4.50).

THE author summarizes the experience of more than 35 years of research in some fundamental aspects of tuberculosis. Having worked with Calmette, Boquet, Bretey, and others, he cites numerous observations concerning the biological properties of BCG and of the various chemical fractions of the tubercle bacillus.

Negre is enthusiastic about the power, both preventive and curative, of an extract of tubercle bacilli (defatted with acetone, then extracted with methyl alcohol) which he believes can exert a favorable influence upon infected laboratory animals and upon certain cases of clinical tuberculosis.

Therapy with various tuberculins and with BCG has been attempted in the past, both

in this country and abroad. The majority of phthisiologists were never enthusiastic for long. The methyl antigen, which the author considers safer and more effective than tuberculin or BCG, may prove helpful in some patients with indolent disease which does not respond to standard treatment. Negre and others recently have combined antigen and antibiotics in their treatment regimens and believe that the results are better than if either modality were used alone.

This volume offers physicians, with ability to read French, some interesting thoughts about often-neglected factors in tuberculosis.

R. C.

THE ESSENTIALS OF MODERN SURGERY. By R. M. HANDFIELD-JONES, M.C., M.S., F.R.C.S., AND SIR ARTHUR E. PORRITT, K.C.M.G., C.B.E., M.A., M.CH., F.R.C.S. 5th ed. Pp. 1276; 649 ills. Edinburgh and London: E. & S. Livingstone, Ltd., 1957 (Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $15.00.

THIS surgical text is designed primarily for the medical student. There are 16 contributors. The book is quite well written, is clear and the type legible. The illustrations are good. There is some discontinuity associated with multiple authors but on the whole, the text is quite complete in that it covers the subjects of general surgery and includes genitourinary work, gynecology, operative gynecology, orthopedics, neurosurgery, as well as general surgery, and nose and throat surgery.

One gets a slightly different point of view about certain processes that are somewhat different from our own. An instance of this is in the treatment of burns in which the authors state that they prefer to use plasma since the use of electrolyte solutions seems to increase to some extent the amount of edema. By and large, the differences are slight and do not in any way detract from the usefulness of the book.

The features which are so attractive in this text are the brevity yet the completeness of coverage of the field of surgery, and the concise statement. I feel this is quite a satisfactory book for medical students and interns, in that the basic fundamentals of surgery are stressed.

R. T.

CIBA FOUNDATION SYMPOSIUM ON BONE STRUCTURE AND METABOLISM. Edited by G. E. W. WOLSTENHOLME AND C. M. O'CONNOR, Editors for the Ciba Foundation. Pp. 299; 121 ills. Boston: Little, Brown & Company, 1956. Price, $8.00.

THIS book comprises an interesting group of papers presented at a Ciba Foundation Symposium entitled *Bone Structure and Metabolism* in July, 1955 The participants represented the outstanding workers in this field and are of international repute. The editors have done a commendable task in collating the material and in presenting it in an orderly fashion. In this volume we are introduced to the fact that bone tissue, more specifically spongy bone, is actually a system exerting contact with tissue fluids, while compact bone contributes to mechanical stability or support. We are given an insight into the structure of bone salts and are acquainted with the differences between the mucopolysaccharides of growing bone and cartilage. Radiosulphur as a tool in the study of formation and metabolism of the ground substance in supporting tissues forms the basis of another presentation. The role of bone citrate in calcification and the role of magnesium deficiency in bone leading to tetany in farm animals are other featured articles. Obviously parathyroid function is not neglected. Each paper was discussed by the expert participants or by the experts attending the Symposium and the editors have given us the benefit of their remarks and their experiences. This is a valuable volume for those interested in bone tissue from its anatomical, physiological, biochemical and clinical aspects.

A. P.

OBSERVATIONS ON KREBIOZEN IN THE MANAGEMENT OF CANCER. By A. C. IVY, PH.D., JOHN F. PICK, S.B., M.D., AND W. F. P. PHILLIPS, M.D., Pp. 88; 5 ills. Chicago: Henry Regnery Company, 1956. Price, $2.50.

IN this small book an attempt is made to justify the use of a new substance, Krebiozen, in the therapy of various types of cancer. If the claims are warranted, it is curious that no clear-cut description of the methods for the preparation of Krebiozen is presented. For instance, on page 8 the statement reads "An organic solvent was used to extract the antiblastic or growth regulating substance from the blood serum." The reviewer has been unable to discover the nature of the organic solvent utilized. It is this type of presentation which renders the work somewhat questionable. Otherwise, the claims made are extraordinary. The substance is said to induce palliative potency in 68% of patients in several different types of cancer.

The conclusion drawn is that Krebiozen possesses oncolytic properties and this has been observed in 50% of patients. The improvements are claimed to be independent of other forms of therapy. The therapy resembles in some aspects that induced by androgens and estrogens. Refractoriness to the substance develops in many patients from 1 to 24 months. It is the belief of the reviewer that if the claims made for Krebiozen are to be justified, a precise and detailed description of its preparation should first be presented, so that verification can be attempted. Pending this state of affairs, only a sense of skepticism can be maintained.

V. M.

THE ADOPTION OF INOCULATION FOR SMALLPOX IN ENGLAND AND FRANCE. BY GENEVIEVE MILLER. Pp. 355; frontispiece and 14 ills. (appearing as a group). Philadelphia: University of Pennsylvania Press, 1957. Price, $6.00.

THIS diligently investigated and well presented study appeals to this reviewer as a truly successful assemblage of the numerous threads that ramify through a complicated subject. The author's excellent training in medico-historical research has already borne fruit in a number of valuable contributions to the subject, so that she is well known by medical historians in this country and abroad.

The ground is covered in 10 chapters by: 1) an introductory background; 2) the new scourge, smallpox; 3) inoculation; 4) royal patronage and inoculation in England; 5) and 6) inoculation through the year 1752; 7) and 8) inoculation on the Continent; 9) the effect of the inoculation theories about smallpox; 10) conclusions that cover revisions in the history of inoculation, changes in the intellectual climate, and demonstration of the success of the method. Of the 4 Appendices, the most interesting is the third on the changing ratio of deaths by smallpox to all other diseases in the eighteenth century. An extensive Bibliography, one of Dr. Miller's special lines of activity, covers 45 pages, where those interested can find plenty of guidance, whether to primary or secondary sources, contemporary or modern, specializing or general.

Among the wealth of significant observations, might be mentioned fallacies about inoculation as demonstrated by use of the statistical method. Also the factors that made inoculation acceptable in Western Europe, such as the increasing fear of the disease extending from the lower classes to the royal families (William of Orange died from it in 1650, his daugter-in-law, Queen Mary in 1694, Louis the XV in 1774, and many others). The frequency of epidemics was increasing, though that of 1681 was said to have had the highest death toll of all. The re-evaluated role of Lady Montague and the part played by the clergy and literary figures such as Voltaire in influencing public opinion, and clearer ideas on the cause of smallpox, are but a few picked almost at random that should be of interest to epidemiologists, sociologists and public health specialists as well as to medical historians. Even semanticists should be intrigued by the horticultural origin of "inoculation," a word originally meaning the process of inserting a bud into a plant as a means of propagation.

While describing the scope of this account of a procedure of prime importance in the development of therapy, the reviewer has already sufficiently indicated his opinion as to its value. It remains but to congratulate the author and the publisher on this meritorious production.

E. K.

THE METABOLIC RESPONSES TO NEONATAL SURGERY. BY PETER PAUL RICKHAM, M.S. (LONDON), F.R.C.S., D.C.H., Consultant Pediatric Surgeon, Royal Liverpool Children's Hospital and Alder Hey Children's Hospital, Liverpool, England; Arris and Gale Lecturer, Royal College of Surgeons of England, 1956. Pp. 93; 12 ills. Cambridge, Massachusetts: The Harvard University Press for The Commonwealth Fund, 1957. Price, $5.00.

THE author presents a careful and detailed study investigating the metabolic changes occurring in 9 newborn infants undergoing selected major surgical procedures. Some 3,000 chemical analyses are recorded in detailed tables and charts. The pattern of the metabolic studies closely follows that of F. D. Moore and M. R. Ball. Although these studies are concerned with newborn infants, the many differences in metabolic responses to surgical trauma of the newborn as compared with the metabolic responses of adults are discussed.

The author has laid down a rather hard and fast pre- and post-operative regimen for infants based on these studies. Due to the inability of most laboratories to carry out these metabolic studies, he has presented a 10th case to illustrate the importance of folowing the basic rules laid down by the recorded investigation, and four biochemical

studies that are needed to carry out satisfactory postoperative management.

This book is a good introduction to the metabolic response of neonatal infants undergoing surgical procedures. S. C.

THE STRUCTURE OF NUCLEIC ACIDS AND THEIR ROLE IN PROTEIN SYNTHESIS (Biochemical Society Symposia Number 14). Edited by E. M. CROOK, University College, London. Pp. 74; 19 ills. London and New York: Cambridge University Press, 1957. Price, $3.75.

THE appearance of the fourteenth number of this excellent series in cloth-bound form is most welcome. This book is made up of papers and appropriate discussions thereof presented at a symposium sponsored by the British Biochemical Society which was held February 18, 1956, at the London School of Hygiene and Tropical Medicine. It is recommended highly as a thoughtful and provocative summary of some of the advances in a rapidly expanding field of investigation.

Dr. N. W. Pirie, who is well known for his pioneering work on the chemistry of viruses, introduced the symposium by pointing up some of the "dangerous assumptions" involved in the extrapolation of fragmentary data to all-embracing theories, especially as regards nucleic acid structure. The current status of knowledge of the "Chemical Structure of Polynucleotides" is reviewed by Dr. R. Markham as the first paper of the symposium. The second, "Molecular Structure of Deoxyribose Nucleic Acid and Nucleoprotein and Possible Implications in Protein Synthesis" was presented by Dr. M. H. F. Wilkins of King's College. Some intriguing suggestions are made as the possible modes of linkage between histone and the helical structure of deoxynucleic acid.

The introduction to the second part of the symposium was given by Dr. J. N. Davidson who reviewed some "Cytological Aspects of the Nucleic Acids." Drs. B. A. Askonas, J. L. Smith and T. S. Work of the National Institute for Medical Research (London) described many interesting relationships in their paper on "Nucleic Acids and Protein Synthesis in Animal Tissues." Dr. E. F. Gale, in the succeeding presentation, "Nucleic Acids and Incorporation of Amino Acids," criticized some of the work with animal tissues and emphasized the problems involved in the interpretation of data on the uptake of radioactive amino acids into various tissue preparations as evidence for protein synthesis. His own important work on the relationships between protein synthesis and various nucleic acid fractions obtained from Staphylococci is also presented.

The final paper entitled "Interrelationships of Nucleic Acid and Protein in the Multiplication of Bacteriophage" was given by K. Burton of Oxford. It includes a review of the work on the T_2, T_4 and T_6 bacteriophage infection of *Escherichia coli*. R. B.

PSYCHOTHERAPY OF THE ADOLESCENT. Edited by BENJAMIN HARRIS BALSER, M.D. Pp. 270. New York: International Universities Press, Inc., 1957. Price, $5.00.

THIS book contains chapters authored by those working with adolescents in different settings such as in an office, in boarding school, in a hospital, and other such situations. The authors tend to agree that treatment of the adolescent requires great flexibility on the part of the therapist; that analysis of the psychodynamics of the biographical past is rarely appropriate or successful. They state that ego support is most important and treatment can usually be shorter in duration than with adults. Balser advocates seeing the parents as part of the therapy and believes that one parent may be treated simultaneously with an adolescent although only rarely could or should both parents be treated along with the adolescent by the same therapist.

There are chapters by a pediatrician and by a headmaster of a school. The total contribution of the book makes it a modern, readable orientation and reference work for the general practitioner, internist, and specialist who is dealing with an increasing number of emotional problems in adolescents. O. E.

CONDITIONNEMENT ET REACTIVITÉ EN ELECTROENCEPHALOGRAPHIE. Edited by H. FISCHGOLD AND H. GASTAUT. Pp. 475; 207 ills. Paris: Masson et Cie, 1957. Price, 5.800 fr.

THIS volume contains the papers presented at an international symposium held in Marseilles in 1955, and devoted to a study of the relationships of the electric activity of the brain to psychologic phenomena. In the first part the cerebral mechanisms involved in conditioning were analyzed electrographically in experimental animals as well as in the human. In the second part, it was attempted to establish correlations between

the type of electric activity and reactions of various organs such as the heart, respiration, autonomous elements of the skin, on the one hand, and the results of psychologic tests (for example, the Rorschach test) on the other. It was found that, for instance, slow waves in a nonpathological recording are often linked with immaturity and poor self-control, while Rolandic beta rhythms are often associated with marked aggressiveness. In the final part dealing with reactivity, the place of cortical electrical activity in the functional architecture of the organism as a whole is elucidated and changes in ontogenesis as well as in pathologic conditions (coma, petit mal and others) are described. The study of these papers that are written in French is facilitated for readers, primarily versed in English, by abstracts in this latter tongue. E. S.

DEXTRAN AND ITS USE IN COLLOIDAL INFUSION SOLUTIONS. By ANDERS GRÖNWALL, Professor of Clinical Chemistry, University of Uppsala, Sweden. Pp. 156; 28 ills. New York: Academic Press, Inc., 1957. Price, $4.00.

THIS small monograph is a clearly written, comprehensive survey of 15 years of research in both Europe and America on dextran as a colloidally active infusion substance by one of the men who introduced it in Sweden in 1942. The problems of its development and use are evaluated and aspects which need further investigation are emphasized. A major portion of the book deals with the chemistry, production, adaptation of molecular size to therapeutic use, the metabolism and serology of dextran. The use of dextran as a plasma expander in experimental shock in animals is discussed. There is a long final chapter on the clinical investigation of dextran, its primary effect as a plasma expander, secondary effects, and untoward reactions. Its usefulness in the treatment of shock, in blood replacement, and in burns in civilian use and in times of disaster is discussed. Other uses, including that of a diuretic in nephrotic edema, are treated. J. G.

LA PUBERTÉ: ETUDE CLINIQUE ET PHYSIOPATHOLOGIQUE. By GUY LAROCHE AND 10 OTHERS. 2nd ed. Pp. 394; 42 ills. Paris: Masson et Cie, 1957. Price, 2.800 fr.

THIS monograph by G. Laroche and ten collaborators deals with problems of puberty very broadly; the scope of the work is apparent from the headings of the sections: Mechanism of Puberty, Puberty and Tuberculosis, Post-pubertal "Mental Anorexia" (we are more familiar with the term anorexia nervosa), The Simple Goiters of Puberty, The Heart in Puberty, Female Infantilism of Puberty, Male Infantilism, Osseous Development and Puberty, Psychologic and Psychopathologic Aspects of the Pubertal Age, Growth and Nutrition. The first edition was published in 1938; Laroche, in the introduction, states that the present publication is in reality not a second edition, but a completely new book. On the whole, this is an authoritative and good book. My major criticism is the absence of an Index. In a work by many authors, the coverage is as would be expected, somewhat uneven. I find the section on Mechanism of Puberty the best; lucid and with a broad and critical coverage of literature. The clinical sections are good; I find the section on Psychology and Psychopathology superficial, verbose, and by far the weakest; note that I am not a psychiatrist. The book will be read with profit and enjoyment by physiologists and clinicians interested in the problems of puberty. K. P.

THE YEAR BOOK OF NEUROLOGY, PSYCHIATRY AND NEUROSURGERY, 1956–1957 SERIES. Neurology edited by ROLAND P. MACKAY, M.D., Professor of Neurology, University of Illinois; Psychiatry edited by S. BERNARD WORTIS, M.D., Professor of Psychiatry and Neurology, New York University; and Neurosurgery edited by OSCAR SUGAR, M.D., Associate Professor of Neurological Surgery, University of Illinois. Pp. 596; 86 ills. Chicago: Year Book Publishers, Inc., 1957. Price, $7.00.

THIS reviewer looks forward every year to reviewing this excellent practical yearbook. The material is almost equally divided between the three specialties. The articles abstracted are taken from journals received between November, 1955, and October, 1956.

Each section is introduced with an evaluation by the author of progress made in that field and the problems which confront the author in selecting articles which would be of interest to the reader.

The abstracts are concise, but contain enough material to adequately describe the subject matter and to stimulate the reader to review the original article if he so desires.

It is impossible to cover the tremendous amount of subject matter. However, anyone who browses through this book will be more

than amply repaid by the wealth and diversity of the material.

As in previous editions, the type is large and the articles are easy to read and the illustrations are clear and complement the text.

This monograph is invaluable to anyone studying or practicing medicine. M. S.

MEDICAL EFFECTS OF THE ATOMIC BOMB IN JAPAN. Edited by ASHLEY W. OUGHTERSON, Clinical Professor of Surgery, Yale University, and SHIELDS WARREN, Pathologist, New England Deaconess Hospital and Professor of Pathology, Harvard Medical School. Pp. 477; 321 ills. New York: McGraw-Hill Book Company, Inc., 1957. Price, $8.00.

THIS volume is a complete presentation of the medical effects of the atomic bomb as observed during years of study by the Joint Commission composed of U.S. military and civilian scientists. There are chapters on The Scope of Damage and the Effects on Medical Care and Facilities, Number and Type of Casualties, Clinical Observations, Hematology, and Pathology of Atomic Bomb Injuries. There are numerous illustrations, many of them in color, and of excellent quality. Based upon the six volumes containing the full reports of the Joint Commission, this book gives in convenient form all the significant material of medical interest, especially from the standpoint of civilian defense. It is, therefore, recommended to all physicians.

R. K.

INDUSTRIAL TOXICOLOGY. BY LAWRENCE T. FAIRHALL, United States Public Health Service. 2nd ed. Pp. 376. Baltimore: The Williams & Wilkins Company, 1957. Price, $10.00.

THIS is the second edition of a concise but inclusive reference book on industrial toxicology. The contents are arranged in two parts, Inorganic Substances and Carbon Compounds, each part being arranged alphabetically by toxic agent. The text material under each toxic substance is arranged as follows: Characteristics, Industrial Uses, Toxicity and Analysis. References to the original literature appear conveniently at the end of the discussion for each substance. The book appears to be as up-to-date as one could expect in view of the rapidity with which new, potentially toxic, products appear. Under no agent is there a section on therapy *per se*, and only brief, occasional mention is made of either symptomatic or specific therapy under the sections titled "Toxicity." More is said, however, about preventive measures in industry. The Index is generally adequate for the trained toxicologist; the average physician, however, might have difficulty finding what he's looking for unless he happens to know the chemical contents of the product concerned. The book should be of undoubted value to the Toxicologist and the Industrial Physician; it may have occasional, limited usefulness as a reference source for the average physician. R. S.

THE ELECTROCARDIOGRAM; ITS INTERPRETATION AND CLINICAL APPLICATION. BY LOUIS H. SIGLER, M.D. 2nd ed. Pp. 312; 195 ills. New York: Grune & Stratton, Inc., 1957. Price, $8.75.

ELECTROCARDIOGRAPHY is being widely used; that implies abuse by those who lack adequate knowledge and critical experience. To convey this, there are available many texts. The one under consideration here is of a practical nature, not overburdening the reader with theoretical considerations, emphasizing the more common conditions. The clearness of the description in text and in captions to the illustrations shows a good integration of the author's knowledge with so much information available in the literature. The backbone of such a teaching text is illustrations; they, so to speak, bridge in a way the gap between symbolic and intimate knowledge; most of them are very satisfactory; some are inadequate when, in the presence of myocardial disease or hypertrophy, only one chest lead is available (see chapters on pericarditis, myocarditis, trauma and congenital heart disease); and there are essentially no illustrations for endocrine, metabolic, and electrolyte disturbances.

H. R.

CLINICAL PROCTOLOGY. BY J. PEERMAN NESSELROD, B.S., M.S., M.Sc.(MED.), M.D., Assistant Professor of Surgery, Northwestern University Medical School. 2nd ed. Pp. 296; 72 ills. Philadelphia: W. B. Saunders Co., 1957. Price, $7.00.

THIS volume succeeds admirably in following the purposes of the author in submitting that part of his experience with diseases of the rectum and anal canal which he feels of value to the general practitioner. The chapter on anatomy is particularly clear so that the pathologic processes developing in

this area are understandable. That portion devoted to diagnosis is well detailed because of its importance. The surgical management of the common inflammatory diseases of the rectum and anal canal is presented in an admirable fashion, emphasizing means to achieve a satisfactory functional result. The text is abundantly and appropriately illustrated by drawings, roentgenograms, and photographs, some of the latter in color.

The treatise bears the stamp of authority because with his keen mind the author stands as an experienced observer and active practitioner in this field. Indeed, this contribution of Dr. Nesselrod is both practical and sound, and can be read to advantage by all practitioners of medicine. H. B.

PERINATAL LOSS IN MODERN OBSTETRICS. By ROBERT E. L. NESBITT, JR., M.D., Professor of Obstetrics and Gynecology, Albany Medical College, Union University. Pp. 432; 108 ills. Philadelphia: F. A. Davis Company, 1957. Price, $12.50.

THERE has been a striking decrease in maternal mortality during recent years but the change in the death rates of infants *in utero* and those newly born have been much less impressive. Nesbitt, who was formerly in charge of the Obstetrical Pathological Laboratory at Johns Hopkins University, has utilized material from that institution as well as from published papers to discuss the entire problem of perinatal mortality and morbidity.

The material is presented in 14 chapters each of which is devoted to a particular cause of infant loss; among these abortion, prematurity, anoxia, birth injury, malformations, infections, hemolytic disease, multiple gestation and ectopic gestation are discussed. Although emphasis is placed upon the actual pathologic causes of death many other aspects of each problem are considered. For instance, the process of implantation and embryonic growth and various maternal factors necessary for normal fetal development are considered in the chapter on abortion. In many instances the obstetric aspects of diagnosis and treatment which must be utilized to prevent death are discussed concisely but completely.

The text is supplemented by 108 illustrations of the gross and microscopic pathologic changes with the various lesions which contribute to infant death. In addition there are 65 statistical tables. The Bibliographies are extensive and obviously include many of the most important contributions concerning each subject.

This is an important volume which should be studied by every physician who does obstetrics or who cares for newborn infants. It should be particularly valuable for residents in obstetrics and practicing obstetricians because it indicates so clearly the causes of perinatal mortality and the manner in which it can be reduced. J. W.

HOSPITAL TREATMENT OF ALCOHOLISM. By ROBERT S. WALLERSTEIN, M.D., AND ASSOCIATES. Pp. 212. New York: Basic Books, Inc., 1957. Price, $5.00.

ONE HUNDRED AND SEVENTY-EIGHT patients suffering with chronic alcoholism were studied over a 2½-year period. The author studied and compared: Antabuse treatment, conditional reflex treatment, group hypnotherapy treatment, and milieu therapy. There is an attempt to correlate the efficacy of the various treatment methods to the personality of the individual patient.

This volume is a model for future research projects in the field of chronic alcoholism. M. B.

MORPHINE AND ALLIED DRUGS. By A. K. REYNOLDS, PH.D., Dalhousie University, Halifax, N.S., and L. O. RANDALL, PH.D., Hoffmann-LaRoche, Inc., Nutley, N.J. Pp. 393; 14 ills. Toronto: University of Toronto Press, 1957. Price, $10.00.

THIS book presents in a single volume a reasonably complete discussion of the pharmacology of morphine and other related and currently available analgesic drugs. In addition to morphine the drugs covered include the natural and semisynthetic derivatives of morphine and also the newer synthetic analgesics. The antagonists to the narcotic analgesics receive relatively brief attention *per se*, although the extent to which they have contributed to the knowledge of the pharmacology of morphine and related drugs is indicated in appropriate places throughout the text. The known facts regarding the pharmacology of this important group of drugs as well as unsolved problems relating to their analgesic and other actions and to their addicting properties are, in the opinion of the reviewer, treated with proper perspective. The book contains extensive Bibliographies placed at the end of appropriate sections and is adequately indexed. The book will undoubtedly be of more interest to pharmacologists than to busy clinicians in search of concise statements of the known

facts regarding the actions of these drugs in man. R. S.

DER ULTRAMIKROSKOPISCHE BAU VON HERZ UND KAPILLAREN. By BRUNO KISCH, M.D., Yeshiva University, New York. Pp. 109; 75 ills. Darmstadt (Germany): D. Steinkopff, 1957. Price, DM 25.

THIS represents a summary of nearly ten years pioneer work in this field, with much new evidence having been gathered since the author, a physiologist and cardiologist, published the electron microscopic histology of the heart, New York, 1951. For fixation, the tissues have to be absolutely fresh (tissues from heart and skeletal muscle of humans were obtained in conjunction with commissurotomy operations); the thickness of the objects is less than one-tenth of a micron, hence one observes only thin discs of any object under consideration. A most detailed description of the fine structures of muscles is given accompanied by superb illustrations. Of particular interest are the sarcosomes (known by light microscopy since 1840, the name given by Retzius in 1890). It is shown that the capacity of striated muscle to perform strenuous and incessant work is mathematically a function of the number of sarcosomes, the highest incidence being found in the heart muscle. Fibrils of the heart and striated muscles, respectively, show identical structure. The capillaries lie in the space between the muscle fibers but do not enter them and they show endothelial prominences. This monograph contains much new histologic information, the physiologic meaning of which will be answered by future investigation.

H. R.

TEXTBOOK OF PATHOLOGY. By STANLEY L. ROBBINS, M.D., Associate Professor of Pathology, Boston University School of Medicine. Pp. 1351; 933 ills. Philadelphia and London: W. B. Saunders Co., 1957. Price, $18.00.

THIS is an excellent textbook of Pathology. To be fully appreciated, it should be read, rather than for the reviewer to pick out a few random paragraphs or chapters for comment. The presentation and orientation are ideal. Each organ or system is preceded by a list of the pathological processes affecting that particular part of the body; then there is brief mention of the normal followed by a discussion of the gross and microscopic features, concluding with the clinico-pathological correlation. The latter is emphasized and makes Pathology a dynamic subject, as it should be. Obviously in any text of this size or in any subject of this magnitude there are statements with which the reviewer might take issue, but these do not detract from the value and the purpose of the book. The printed page is easy to read and the illustrations are well chosen. Both Dr. Robbins and the publisher are to be congratulated. Five chapters of the book have been written by collaborators, who are experts in their particular fields. Dr. Robbins has stated in his preface that this textbook has been written for students and clinicians and in the succeeding chapters he ably fulfills this mission.

A. P.

MENTAL DEFICIENCY. By J. E. W. WALLIN, PH.D. Pp. 200. Brandon, Vermont: Journal of Clinical Psychology, 1957. Price, $5.00.

THE person studying the subject of mental deficiency will find this book a valuable digest of the basic problems in the field. The author presents our present-day knowledge of the subjects: fecundity of the mentally deficient; the relation of mental deficiency to defective progeny; the relation of gene injury to mental deficiency, the relation of mental deficiency to criminality and sex delinquencies; the socio-occupational efficiency of mental deficients and alcoholism among them; the ultimate aims of constructive work in the field of mental deficiency.

This is an excellent up-to-date reference book for students and investigators interested in the study of the problems that come within its scope. An excellent and extensive reference list enhances the value of the book. M. B.

SYNOPSIS OF OBSTETRICS. By JENNINGS C. LITZENBERG, M.D., Late Professor Emeritus of Obstetrics and Gynecology, University of Minnesota Medical School. Revised by CHARLES E. MCLENNAN, M.D., Professor of Obstetrics and Gynecology, Stanford University School of Medicine. 5th ed. Pp. 401; 163 ills. St. Louis: C. V. Mosby Co., 1957. Price, $6.00.

THE popularity of "Synopsis of Obstetrics" is indicated by the fact that this is the fifth edition to appear since it was first introduced in 1940. The present author, who aided Litzenberg in the preparation of the early editions and who has been entirely responsible for recent ones, has had many years experi-

ence in teaching medical students toward whom the book is directed.

The arrangement of the material is much like that in larger standard texts but because of the nature of the book it is of necessity compressed and didactic obviously indicating the methods preferred by the author in his own practice. Considerable stress is placed on subjects such as the diagnosis of pregnancy, normal labor and others which are so important to the student and family doctor.

The major advantage of this book is that it describes methods for managing the common obstetric situations which are presented briefly yet reasonably completely. It does have disadvantages, however, while it provides the student with accurate basic information a synopsis which is so easy to read discourages his study of more inclusive texts. In his effort to maintain brevity the author at times advises treatment in terms, such as "appropriate antibiotic therapy," which are too general for students.

A synopsis of this sort is an excellent supplement to reading from a more inclusive text but it will hardly do by itself. It is most useful to medical students and possibly interns. Its main value to more advanced physicians is to provide a rapid means of reviewing obstetrics. J. W.

THE EARLY DIAGNOSIS AND TREATMENT OF ACOUSTIC NERVE TUMORS. BY J. LAWRENCE POOL, M.D., Professor of Neurosurgery, Columbia University, and ARTHUR A. PAVA, M.D., Assistant Neurosurgeon, Wesson Memorial Hospital, Springfield, Mass. Pp. 161; 33 ills. and 1 color plate. Springfield, Ill.: Charles C Thomas, 1957. Price, $5.50.

IN this compact monograph, the authors stress the early diagnosis and treatment of acoustic nerve tumors. They present historical data and discuss the histopathology of these lesions. The symptoms and signs are presented in an orderly manner.

Diagnostic procedures such as skull roentgenograms, encephalography, ventriculography, arteriography, electroencephalography, cerebral spinal fluid evaluation and audiometric tests are presented in their proper importance with regard to the diagnosis of these lesions. The authors cite atypical cases and describe operative techniques and postoperative management.

The monograph is well illustrated. There are numerous tables and gross and microscopic photographs of the acoustic neurinomas. The Roentgen-ray plates are diagnostic and well chosen.

This book is of interest to the neurologist, neurosurgeon, and otologist. It will be particularly helpful to residents in neurological surgery. M. S.

OUTLINE OF FRACTURES INCLUDING JOINT INJURIES. BY JOHN CRAWFORD ADAMS, M.D. (LONDON), F.R.C.S. (ENGLAND), Consultant Orthopedic Surgeon, St. Mary's Hospital, London. Pp. 248; 218 ills. Edinburgh and London: E. & S. Livingstone, Ltd., 1957 (Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $6.50.

THIS text is designed mainly for medical students, general practitioners, physiotherapists and student nurses. The author concisely covers the principal features of common fractures and dislocations as to anatomy, clinical features and complications. The accompanying illustrations are abundant for such a text and certainly well chosen. It is also apparent that the author favors conservatism in fracture management, a not too common attitude today. Operative intervention, when indicated, is on sound grounds. The author is Assistant Editor of the Journal of Bone and Joint Surgery. This experience has certainly rubbed off in this lucid outline, a most worthwhile text. A. S.

PRÉCIS DE BACTÉRIOLOGIE MÉDICALE. BY PIERRE GASTINEL, Faculté de Medécine de Paris. 2nd ed. Pp. 1244; 163 ills. and 1 color plate. Paris: Masson et Cie, 1957. Price, 6700 francs (one volume).

THE format and general arrangement of material of this textbook resembles that of Topley and Wilson's well-known English volume. The content, however, is not the same; as the author states in his title, this is a summary of medical bacteriology. The author's understanding of the subject is presented without benefit of literature citations, a method of text writing which produces a smooth and easy style but separates the product from the comprehensive reference books like Topley and Wilson's.

The scope is bacteriology, virology, and immunology; mycology and parasitology are omitted. Also included are selected methods for the collection and laboratory examination of clinical material. Although Prevot's nomenclature is favored over Bergey's, the American user would have no difficulty identifying

species by name (for example, *Welchia perfringens*). Many of the illustrations, and particularly the drawings, are inadequate, the handling of bacterial physiology is superficial and there is an occasional misprint such as Beuner for Bruner on page 409. The reason for sandwiching the chapter on pleuropneumonia-like organisms between that on nucleic acids and another on the effects of physical and chemical agents is not apparent to the reviewer. In his preface the author makes much of ("l'ésprit physio—pathologique"), a point of view not only commendable but practically essential to a good present day textbook of bacteriology which this one in many ways appears to be.

E. S.

AN ATLAS OF THE COMMONER SKIN DISEASES. BY HENRY C. G. SEMON, M.A., D.M. (OXON.), Consulting Physician for Diseases of the Skin and Former Lecturer to Post Graduates, Royal Northern Hospital, London. Revised with the Collaboration of HAROLD T. H. WILSON, M.A., M.D., (CANTAB). 5th ed. Pp. 375; 153 ills. in color. Baltimore: Williams & Wilkins Company, 1957. Price, $20.00.

THIS well-known Atlas of the Commoner Skin Diseases has gone through four previous editions, a fact which speaks for the wide reception of this work. The fifth edition, enlarged and revised, had the assistance in its preparation of Dr. Wilson. The contents include many of the commoner diseases arranged alphabetically, followed by a smaller listing of some less common processes. The text is up-to-date and adequate for an atlas. The chief feature, the illustrations, are generally good to excellent. This new edition merits the consideration given its four predecessors.

H. B.

THERAPEUTIC EXERCISE FOR BODY ALIGNMENT AND FUNCTION. BY MARIAN WILLIAMS, PH.D., AND CATHERINE WORTHINGHAM, PH.D. Pp. 127; illustrated. Philadelphia: W. B. Saunders Co., 1957. Price, $3.50.

THIS clear and almost cryptically written monograph is exactly what the authors state it is in their preface, namely, a manual designed for the use of all persons dealing with body alignment and function. It should serve equally well the orthopedic surgeon, physiatrist, industrial surgeon, and physical therapist. In addition, the medical student may well find it his only source of accurate material on body mechanics.

The drawings are clearly conceived, and in a subtle fashion, make the author's point. The Bibliography is well chosen and well edited. The exercises are clearly described and plainly demonstrated. In short, the text is good. The only criticism would be the Appendix, which except for emphasizing some facts from the text, is mainly an anatomic demonstration. It might better have been incorporated into the text or perhaps made into a separate section on muscle testing. At any rate, as the authors state regarding the Appendix, "The reader who wishes to study this material in more detail should consult a textbook of anatomy." The book, however, accomplishes the purpose of the authors in a very admirable fashion.

H. S.

METHODOLOGY OF THE STUDY OF AGEING. Ciba Foundation Colloquia on Ageing, Vol. 3. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.CH., AND CECILIA M. O'CONNOR, B.Sc. Pp. 202; 47 ills. Boston: Little, Brown & Co., 1957. Price, $6.50.

THIS volume represents the record of the third annual colloquium on ageing, held in July, 1956, and with 28 participants. The emphasis is on the biological approach and the gerontologist will find much that is of challenging interest. Of particular value are the fully recorded free discussions by the participants.

R. K.

CLINICAL LABORATORY DIAGNOSIS. BY SAMUEL A. LEVINSON, M.S., M.D., PH.D., Director of Laboratories, University of Illinois Research and Educational Hospitals, Chicago, and ROBERT P. MACFATE, CH.E., M.S., PH.D., Chief, Division of Laboratories, City of Chicago Board of Health. 5th ed. Pp. 1246; 244 ills. and 13 plates, 11 in color. Philadelphia: Lea & Febiger, 1956. Price, $12.50.

THE 5th edition of this textbook of Clinical Laboratory Diagnosis maintains the over-all excellence of its predecessors. Much progress has been made since the last edition, and the authors have revised and rewritten pertinent sections in order to incorporate these advances. An important feature is the utilization of the newer terminology in hematology as recommended by the Committee on Hematology of the American Society of Clinical Pathologists. Also, the section on Blood Typings and Blood Bank has been completely revised with use of the terminology recommended by the National Institutes of Health.

The methods chosen for detailed description are generally accepted, and are clearly presented. The illustrations are numerous and, for the most part, excellent. The color plates of blood cells, however, leave much to be desired.

This volume should continue to hold an important place in the teaching of clinical pathology to medical students, and offers an up-to-date reference text for the practicing physician. C. Z.

LIVER: STRUCTURE AND FUNCTION. By HANS POPPER, M.D., PH.D., Director, Department of Pathology, Cook County Hospital, Chicago, and FENTON SCHAFFNER, M.S., M.D., Co-chairman, Department of Medicine, Woodlawn Hospital. Pp. 777; 204 ills. New York: McGraw-Hill Book Co., Inc., 1957. Price, $20.00.

THIS is a well-written, well-illustrated monograph, the joint product of a pathologist and a clinician. Part I deals with normal structure and function. Part II is devoted to pathological phenomena in the hepatobiliary system. Part III is a clinical study of hepatic structure and function. Part IV deals with diffuse diseases of the liver; Part V, focal diseases of the liver; Part VI, tumors of the liver and biliary tree; and Part VII deals with internal and external environment and the liver. The Bibliography includes 3,735 references. The book should prove an excellent source book on the liver in health and disease. R. K.

HEALTH AND MEDICAL CARE IN NEW YORK CITY. A REPORT BY THE COMMITTEE FOR THE HEALTH INSURANCE PLAN OF GREATER NEW YORK. Pp. 289; 30 ills. Cambridge, Massachusetts: Harvard University Press for The Commonwealth Fund, 1957. Price, $7.50.

THIS is a statistical study of multiple factors concerned with the sickness and health of a large group of members of the Health Insurance Plan of Greater New York, as contrasted to a similar nonmember group. This study was performed in a precise and careful manner and represents a fairly massive undertaking. It is of especial value to those interested in health insurance plans, public health officials, and the like. W. S.

AGEING IN INDUSTRY. By F. LE GROS CLARK AND AGNES C. DUNNE. Pp. 150; 2 ills. New York: The Philosophical Library, Inc., 1956. Price, $7.50.

THE authors have studied the employment figures by age groups for thirty-two occupations in Britain to determine the survival rates of workers engaged therein. Whereas 75 to 85% of makers of watches and clocks or musical instruments or workers in precious metals are able to continue working past sixty-five, only 5 to 15% so continue in coal mining. The book provides useful data in this important aspect of gerontology. R. K.

PROBLEMS OF AGING. Edited by ROBERT L. CRAIG, M.D. Pp. 221; 51 ills. New York: New York Academy of Medicine, 1956 (Distributed by George Eliot, New York). Price, $3.50.

A COLLECTION of nineteen papers presented by twenty-six authors at a symposium at the 28th Annual Graduate Fortnight of the New York Academy of Medicine. They represent a cross section of current thinking in geriatrics. R. K.

SURGERY OF THE ANUS, ANAL CANAL AND RECTUM. By E. S. R. HUGHES, M.D., M.S., F.R.C.S., Surgeon to Out-Patients, The Royal Melbourne Hospital, Melbourne, Australia. Pp. 294; 276 ills. Edinburgh and London: E. & S. Livingstone, Ltd., 1957 (Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $10.00.

IT has been a pleasure to review the recent treatise on "Surgery of the Anus, Anal Canal and Rectum" by Dr. Hughes. Particularly noticeable is the author's modesty in his discussion which is always an admirable attribute. The context reflects the writer's excellent training received at St. Mark's Hospital in London which represents the "Mecca" of rectal and colonic surgery. The chapter on surgical anatomy is especially outstanding. It is good to find additional reference to the importance of the inferior mesenteric artery and its branches in relation to lymph node dissections. One might gather that the "point of Sudek" is deserving of special comment but this reviewer feels certain that this was not the intent of the author since this point is quite irrelevant and has been discarded for a decade or more. It would appear that preservation of the lower sigmoidal arteries is necessary for viability in resections of the sigmoid colon. Let it be repeatedly emphasized that such is unnecessary since the reviewer in over one thousand patients has always found the blood supply from the in-

ferior hemorrhoidal arteries and its tributaries to be adequate.

The chapters on anorectal suppuration, fistula and sinuses related to the anus are lucidly presented. Hemorrhoids and their management, as well as prolapse of the rectum, are written of in such fashion that the reader is able to apply them in his daily practice. The chapter on benign and malignant tumors is presented in a classical and illuminating fashion. Especially enlightening are the historical notes appended to the text.

H. B.

THE SPECIALTIES IN GENERAL PRACTICE. Edited by RUSSELL L. CECIL, M.D., Professor of Clinical Medicine Emeritus, Cornell University Medical College, and HOWARD F. CONN, M.D., Fellow, Department of Physiology, Baylor University College of Medicine. 2nd ed. Pp. 780; 76 ills. Philadelphia: W. B. Saunders Co., 1957. Price, $16.00.

THIS is the second edition of a work for which there appears to be a real need and demand. Some fifteen specialists have prepared sections for the ready reference of the practitioner in the management of the less serious problems in the various special fields. There are chapters on Minor Surgery, Orthopedic Surgery, Fractures and Dislocations, Urology, Diseases of the Anus, Rectum and Colon; Gynecology and Obstetrics, Pediatrics, Ophthalmology, Diseases of the Nose and Throat, Diseases of the Larynx, Bronchi and Esophagus, Otology, Dermatology and Syphilology, and Psychiatry. The authors have achieved a high degree of success in their effort. There are occasional duplications and coverage is at times too scant. In this edition, Doctor Conn has been associated with Doctor Cecil as editor.

R. K.

ORTHOPEDIC SURGERY IN INFANCY AND CHILDHOOD. BY ALBERT BARNETT FERGUSON, JR., M.D., Silver Associate Professor of Orthopedic Surgery, University of Pittsburgh. Pp. 508; 504 ills. Baltimore: Williams & Wilkins Company, 1957. Price, $15.00.

THIS text is principally written by Doctor Ferguson. However, important sections are by contributors, five in number, highly qualified in their respective fields. The text aptly covers most pure orthopedic subjects encountered in infants and children. As the authors admit, fractures in children are excluded in view of Doctor Blount's text on this subject, published in 1954.

The text is of considerable scope. Common problems encountered in the practice of orthopedics as well as many odd and unusual syndromes are included.

The sections on congenital hip dislocation, scoliosis and congenital hand deformities are excellent. The author's concept of pronated feet associated with toeing in is open to question, as is his management of this condition.

Surgical technique is avoided; however, indications for surgery where needed are correctly mentioned. The illustrations are abundant and excellent.

In general this is a worthwhile text for the orthopedic resident and is certainly a must for the orthopedist whose practice is concerned with children.

A. S.

NEW BOOKS

Emotional Illness: How Families Can Help. BY KARL R. BEUTNER AND NATHAN G. HALE, JR. Pp. 158. New York: G. P. Putnam's Sons, 1957. Price, $2.75.

THIS small and readable book discusses some of the basic causes of emotional illness in a clear way. The authors tell how sick emotions such as fear, anger or guilt are prone to arise in a family member, how they are to be understood and dealt with. They also discuss the modern psychiatric and psychotherapeutic methods in a manner that should bring the greatest understanding and cooperation between doctor and family. Definitely belongs with the acceptable books of this type.

O. E.

Death of a Man. BY LAEL TUCKER WERTENBAKER. Pp. 181. New York: Random House, 1957. Price, $3.50.

THIS is a book about a man who discovers in his early fifties that he has cancer. The story of how he met and dealt with this fact is told by both himself and his wife, and includes events up to the very end. They both had in common a mature love for each other combined with a love of life and neither faltered in trying to include death as one of life's phenomena. They tried to deal with dying in a dignified and courageous way and most readers will say they succeeded.

The facts are stark and require a strong sense of realism and a humanistic philosophy to follow comfortably. Good reading for doctors who have to deal with seriously ill and dying people. An interesting medical story but also an unusual love story if there ever was one.

O. E.

Thyroid and Iodine Metabolism. Report of the Twentieth Ross Pediatric Research Conference. Edited by G. J. BARBERO, M.D.; 40 participants from many institu-

tions. Pp. 77; 10 ills. Columbus, Ohio: Ross Laboratories, 1957.

THIS conference report is authoritative and timely. Participants are well selected from among the most careful and active investigators in the field. Reports and discussion center particularly on these subjects: (1) Thyrotropic hormone (TSH) production, and rate and mode of distribution and utilization. (2) Exophthalmos Producing Substance (EPS). (3) Thyroid hormone synthesis and secretion, normal enzymatic mechanisms and abnormalities observed in goitrous cretins, patients with endemic goiter and their families. (4) Thyrotoxicosis, long term comparative studies of Graves' disease as differentiated from toxic nodular goiter. (5) Thyroid therapy with special reference to newborn cretins. Both the reports and discussions are concise, oriented primarily to workers in this area. Occasional errors and ambiguity of expression as well as the lack of a Bibliography may pose difficulties for readers not familiar with recent developments.

W. P.

X-Ray Technology. By CHARLES A. JACOBI, B.Sc., R.T. (A.R.X.T.), M.T.(A.S.C.P.), Head, X-ray Technology, Oregon Technical Institute, Oretech, Oregon, and D. E. HAGEN, R.T. (A.R.X.T.), Instructor, Oregon Technical Institute, Oretech, Oregon. Pp. 410; 320 ills. St. Louis: C. V. Mosby Co., 1957. Price, $9.75.

THIS is a practical manual of basic information and techniques used in the field of diagnostic roentgenology. It should prove to be a useful guide in the teaching of x-ray technique and a helpful text for the technician in training.

G. B.

Freud and Contemporary Culture. Edited by IAGO GALDSTON, M.D. Pp. 99; 1 ill. New York: International Universities Press, Inc., 1957. Price, $3.00.

THE New York Academy of Medicine offers these six essays as part of their Freud Centenary Celebration. The essayists are Kenneth E. Appel, Roy R. Grinker, Paul V. Lemkau, Gregory Zilboorg, Clydek Kluckholm and Iago Gladston. The volume contains a foreword by Thomas C. Peightal and an introduction by Paul H. Hoch.

Freud has effected the entire fabric of our intellectual, esthetic and medical culture. The essays are both appreciative and critical of Freud and his work.

Zilboorg points out that the work of Freud is too complex to allow for a proper evaluation of his place in medical psychology only one hundred years after his birth and seventeen years after his death.

M. B.

The Caricature of Love. By HERVEY CLECKLEY, M.D., Clinical Professor of Psychiatry and Neurology, Medical College of Georgia. Pp. 319. New York: The Ronald Press Company, 1957. Price, $6.50.

LITERARY media present perverse psychic reactions, particularly homosexuality, as normal or even as a superior way of life. Psychiatric and psychologic literature often fall into the same error. Based entirely upon the author's personal views on how life should be lived, this book is essentially a condemnation of human nature. Interestingly enough, although essentially an appeal for idealism, some of the descriptions in this book tend to be lewd.

The style of this book is painful. The following sentence, referring to homosexuality, is typical of the book: "Many laymen who discuss the subject seriously, particularly those who are aware of current intellectual and artistic fashion, of the esthetic climate of our times, present opinions which emphasize the important creative work done by famous inverts and also what they often believe is evidence from psychiatry that, after all, there really is not much that is seriously pathologic about homosexuality."

M. B.

Report of Study Group on the Ecology of Intermediate Snail Hosts of Bilharziasis. WHO Technical Report Series No. 120. Pp. 38. Geneva: World Health Organization, 1957. Price, $.30.

Closed Ranks. By ELAINE CUMMING AND JOHN CUMMING. Pp. 158. Cambridge, Massachusetts: Harvard University Press for The Commonwealth Fund, 1957. Price, $3.50.

THE authors, a sociologist and a psychiatrist, have related an exciting story of an experiment in mental health education. This experiment was performed in a Canadian town, using a demographically similar town as a control. A reasonably intensive six months effort was made by a team to alter the attitude of the town populace toward patients returning from mental hospital confinement. In spite of this effort being performed in a careful and diplomatic manner, the townspeople became quite hostile to the educational team members. By the use of interviews and questionnaires it was found that no attitudinal changes had occurred in the experimental town, and this paralleled the lack of change in attitude toward mental illness in the control town. The experiment is analyzed provocatively from both the sociologic and the psychiatric viewpoints.

W. S.

Epidemiology. Bulletin World Health Organization, No. 1–2, 15, 1, 1956. Pp. 361; illustrated. Geneva: World Health Organization, 1956. Price, $4.00.

THIS volume contains data on the world-wide incidence of cancer of the breast and female genital tract, poliomyelitis in 1954, accident mortality among children, protein malnutrition in Brazil, schistosomiasis in British Africa, virus meningo-encephalitis in Slovenia, botulism as a world health problem, viral and rickettsial infections, endemic goiter in Hungary, Q fever in birds, poliomyelitis in Turkey.

R. K.

Accidents in Childhood. Facts as a Basis for Prevention. WHO Technical Report Series, No. 118. Pp. 40; 7 ills. Geneva: World Health Organization, 1957. Price, $.30.

NEW EDITIONS

A Therapeutic Index. By C. M. Miller, M.D.(Lond.), Consultant Physician, Sefton General Hospital, Liverpool; and B. K. Ellenbogen, M.D.(L'pool), Consultant Physician, St. Catherine's Hospital, Birkenhead, and Mill Lane Hospital, Wallasey. 2nd ed. Pp. 156. London: Bailliere, Tindall and Cox, 1957 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $3.50.

The authors have attempted to provide a guide to the treatment of many of the common and some of the less common conditions met with in medical practice. This pocket-sized manual leaves much to be desired. For instance, there is no mention of the versenate compounds in lead poisoning, only a brief mention of prednisone, no mention of novobiocin, magnamycin, and other newer antimicrobials. The corticoids are not discussed in serum sickness. Urethane is not included in the treatment of myeloma. Intrathecal penicillin is recommended for meningitis. Many of the drugs described are not familiar to those in this country. This book is inferior to many excellent volumes on therapy and it has little use as a work of reference. It is not recommended. W. L.

World Medical Periodicals. Prepared by L. T. Morton under the auspices of a Committee jointly sponsored by the World Medical Association and the International Union of Medical Press. 2nd ed. Pp. 340. New York: World Medical Association, 1957. Price, $6.00.

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